DECEMBER 1959

BRAIN

VOL. 82, PART 4.

CLINICO-PATHOLOGICAL CONSIDERATIONS OF TEMPORAL LOBE EPILEPSY DUE TO SMALL FOCAL LESIONS

A STUDY OF CASES SUBMITTED TO OPERATION

BY

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RECENT developments in the surgical treatment of long-standing and intractable epilepsy of temporal lobe origin have stimulated interest in the underlying pathological processes. These may comprise a wide range of lesions including traumatic and degenerative processes arising at various age periods, as well as neoplasms both large and small, and also vascular malformations. Cases due to large space-occupying lesions form a minority and can generally be recognized pre-operatively by their clinical features or by the neuroradiological investigations. If such cases are then excluded from further consideration, it would appear that in two-thirds of cases of intractable temporal lobe epilepsy submitted to operation the underlying pathological cause is a diffuse sclerosis particularly of the mesial portion of the temporal lobe that usually dates from infancy, while in the remaining one-third it is apparently due to small focal lesions of great pathological diversity. Several papers dealing with mesial temporal lobe sclerosis have recently appeared (incisural sclerosis—Earle, Baldwin and Penfield, 1953; pararhinal sclerosis—Gastaut, 1954; hippocampal-uncinate amygdalar sclerosis—Cavanagh, Falconer, and Meyer, 1958) and its ætiology and significance have been widely discussed.

On the other hand, the small focal lesions have received scantier consideration, although when regarded from a practical standpoint they are of scarcely lesser importance. For instance, not only are the cases in this group quite common, but the presence of a focal and thus of a potentially removable lesion has not infrequently been entirely unsuspected before operation despite many years of focal seizures and careful clinical investigation. Moreover, as a corollary to this, cases in

XUM

this group tend to respond well to surgery by comparison with those cases with more diffuse changes. Further, these focal lesions are sometimes of very restricted extent and thus may be of value in throwing some light on the mechanisms of epilepsy and the contents of the aura exhibited. Finally they are of interest for their histological variety.

Case Material

We have therefore selected for study some 23 cases of small focal lesions, particulars of which are listed on Table I. We realize that the

Table I.

SUB-DIVISIONS OF SMALL FOCAL LESIONS: GENERAL CORRELATIONS IN 23 CASES

PATHOLOGICAL GROUP	NEOPLASMS			VASCULAR MALFORMATIONS	CORTICAL SCARS WITH OR WITHOUT AMMON'S HORN SCLEROSIS	MISCELLANEOUS	
	Glioma	Meningioma	Cholesteatoma			Vascular Degeneration	Tuberous Sclerosis
Number of Cases	11	1	1	2	5	2	1
	13					3	
Mean duration of Epilepsy before operation (yrs.)	8			17	12	3	
Mean age at operation (yrs.)	31			41	28	45	
Result of operation on Epilepsy 2-7 yrs. follow-up:							
Fit-free	9			2	3	-	-
Occasional Fits	2			-	1	-	1
50% Improved	2			-	-	1	-
Not Improved	-			-	1	1	-

numbers are small and that as 14 of the cases were referred from psychiatric hospitals or clinics and only 9 from general hospitals or neurological clinics, the series of cases must be regarded as selected. They have, however, been under study for a long time, and as we know of no other similar series, some useful purpose may be served by considering them now, although for the reasons just stated they may not occur in a similar proportion of cases of temporal lobe epilepsy as a whole.

All our cases were examples of temporal lobe epilepsy exhibiting seizures of psychomotor type which had proved resistant to drug therapy and which had often been present for many years. Moreover in them the usual pre-operative clinical and neuroradiological investigations would be considered (in most hospitals) as excluding a space-occupying lesion. Indeed 5 of the cases, all with small neoplasms, had been referred for surgery a few weeks previously to various neurological

XUM

centres, but at these centres the suitability of the cases for operation had not been recognized. The basis of selection of our cases for operation was largely dependent upon the electroencephalographic findings, for which we are indebted to our colleagues in the Department of Clinical Neurophysiology of the Institute of Psychiatry (Hill, 1953; Pampiglione and Kerridge, 1956; Kennedy and Hill, 1958).

22 of the 23 cases were found among some 70 patients submitted to an anterior temporal lobectomy because no circumscribed focal lesion was visible on the surface of the brain exposed at operation. Care was taken in all these cases to excise the resected temporal lobe in one piece in order to facilitate subsequent pathological and anatomical study (Falconer, 1953 and 1958; Falconer *et al.*, 1955). This, together with the subsequent thorough examination of the material using celloidin technique, were important steps leading to the recognition of many of the smaller lesions. But for this care many of the smaller tumour-like nodules and several of the cortical scars would undoubtedly have been missed. In the remaining 1 of our 23 cases a small lesion Case WOO—(cholesteatoma) was seen on the surface of the exposed brain and removed without resection of brain tissue—yet in this case before operation an experienced radiologist had reported that the air-encephalograms ruled out a space-occupying lesion and were in favour of an atrophic lesion affecting the temporal lobe.

A perusal of Table I shows the underlying lesions can be classified into four subgroups—neoplasms, vascular malformations, cortical scars, and miscellaneous lesions—and that for the most part the results of surgery are good. The clinical features of each subgroup will now be discussed in turn.

Pathological Subgrouping

A. Neoplasms.—Table II lists 13 cases which had small neoplasms, 11 being gliomatous in nature, and 1 each a meningioma and a cholesteatoma. The neuroglial tumours are of several types, and the detailed histological characteristics of 8 of them have been described in a separate communication (Cavanagh, 1958). All 8 were relatively small, and despite long clinical histories invasion of the surrounding brain or overlying meninges was minimal. Evidence has been presented to suggest their possible hamartomatous origin. Of the remaining 3 cases 2 (cases WAK and HAR) were typical oligodendrogliomas and 1 (case EWA) was an astrocytoma; all 3 were extensively involving the mesial portions of the temporal lobe. In this paper we shall not illustrate the microscopic appearances of our cases, as many of them have already been illustrated elsewhere (Meyer, Falconer, and Beck, 1954; Meyer, 1956; Cavanagh, 1958).

XUM

TABLE II.

CLINICO-PATHOLOGICAL DATA OF SMALL NEOPLASMS

PATIENT AGE, SEX	LESION	SITUATION	PRE-OPERATIVE CLINICAL FEATURES: Duration of Psychomotor Epilepsy (yrs).	Plus Grand Mal	Personality	AIR-ENCEPHALOGRAMS	POST-OPERATIVE FOLLOW-UP: Duration (Yrs.)	Epilepsy	Personality
SIN 2½, F	Solitary glioma - oligo-astrocytoma	Middle, inferior and fusiform gyrus	1	No	Aggressive	Small calcified lesion not deforming ventricles	5	Fit-free	Improved
KEI 14, F	- do -	Amygdala, uncus and hippocampal gyrus	6	No	Aggressive	Affected hemisphere slightly small	7	Fit-free	Improved
MIE 23, M	Solitary glioma-ganglioglioma	- do -	11	Yes	Inadequate	- do -	3	Fit-free	Improved
LIB 16, M	- do - also Ammon's horn sclerosis	- do -	12	No	Aggressive	Slight distortion of affected temporal horn	2	Fit-free	Improved
MAR 32, M	Solitary glioma - oligodendioglioma	Fusiform gyrus	14	No	Normal	Normal	4	Very occasional seizures	Still Normal
WAK 56, M	- do -	Amygdala, middle, inferior, fusiform and hippocampal gyri	6	No	Depressive	Moderate dilatation of contra-lateral temporal horn	4	Very occasional seisures	Improved
HAR 51, F	- do -	- do -	11	Yes	Aggressive	Slight displacement of affected temporal horn	4	Improved 50%	Slight Improvement
EWA 35, F	Solitary glioma - astrocytoma	Amygdala and middle temporal gyrus	1	No	Hysterical	- do -	2	Improved 50%	Slight Improvement
VAL 23, M	Solitary glioma - spongioblastoma	Fusiform gyrus	3	No	Normal	- do -	5	Fit-free	Still Normal
GUL 48, F	Solitary tumour - meningioma	Hippocampal gyrus and uncus	10	No	Hysterical	- do -	3	Fit-free	Slight Improvement
WOO 46, M	Solitary tumour - cholesteatoma	Middle temporal gyrus	2	No	Normal	Normal	2	Fit-free	Still Normal
MUN 35, M	Multifocal gliomas - oligo-astrocytomas	Amygdala, uncus, inferior and fusiform gyri	11	No	Inadequate	Affected hemisphere slightly small	3	Fit-free	Improved
STA 19, M	- do -	Amygdala, uncus, hippocampal, and fusiform gyri	14	No	Feeble-minded	Slight displacement of affected temporal horn	2	Fit-free	Improved

Clinical and pathological descriptions. (Throughout the course of the several papers published by our group on temporal lobe epilepsy we have kept to the convention that each case is designated by the first three or four letters to simplify reference from one paper to another.)

8 cases were males and 5 females, and their ages ranged from 2½ to 56 years with an average of 31 years. Again the ages of onset of epilepsy ranged from 1½ to 50 years, while the average duration of epilepsy before operation was eight years. In all the cases seizures of psychomotor type had occurred, while only in 2 was there a history of *grand mal* (major convulsions). In none of the cases were there clinical features of raised intracranial pressure, the symptoms being purely those of epilepsy or often also of behavioural disturbance. Generally the lateralization of

the lesion before operation was made primarily on electroencephalographic grounds, and therefore these aspects will be discussed more fully in a later part of this paper. It is interesting that even in retrospect it is possible to suspect the correct lateralization of the tumour by air-encephalography or by carotid arteriography in only 8 of the 13 cases. In 7 of these cases there was a very slight but suspicious degree of compression, displacement, or distortion of the affected temporal horn revealed by careful air encephalography, while one was partially calcified, but as 4 of these particular cases had had their radiographic studies passed as within normal limits at other neurological centres just prior to their admission to our unit, we have included them in this group. Even in health there are slight variations between the two temporal horns (Van Buren, Baldwin, and Alvord, 1956). In contrast, in the remaining 5 cases of the 13 (Cases KEI, MIE, MAR, WAK, and MUN) all cases of neoplasm, there appeared to be a slight actual reduction in size of the ipsilateral hemicranial vault or cerebral hemisphere.

Furthermore, even in 2 of the 8 cases (Cases LIB and WOO), in which there was slight but suspicious indentation of the ipsilateral temporal horns, there was none the less slight relative smallness of the ipsilateral hemicranium, while in 1 of these 2 cases (Case LIB) the contralateral limbs were slightly smaller than those on the side of the lesion. All the features lend support to the view that the origin of these tumours date back to early childhood, or even prenatal life.

The results of surgery in this group are particularly gratifying for all cases were benefited and 9 of the 13 were rendered completely fit-free. Although histologically these tumours were predominantly gliomatous, and although none of them received roentgen ray therapy postoperatively, there have not appeared as yet, in the follow-up period of from two to seven years, any overt signs of recurrence of neoplasm. Indeed, in 1 case, an astrocytoma (Case EWA) where seizures were still present, although much less frequent, recent arteriographic and air-encephalographic studies have shown evidence of absence of the temporal lobe rather than the presence of a space-occupying lesion.

These results of surgery are particularly remarkable, as in only 4 of the cases (Cases MAR, VAL, GUL, and WOO) were the tumours so restricted in size and so situated in the temporal lobe as to make their total extirpation a likely event. In the remaining cases the plane of section usually skirted part of the tumour. The absence of any suggestion of recurrence in a postoperative follow-up of from 2 to 7 years therefore implies a remarkable degree of indolence that is worthy of a longer term study. In this context it is instructive, perhaps, to recall that histories of focal epilepsy of longer than eight years were encountered in about 12 per cent of a large series of gliomas studied by Penman and Smith (1954). It is conceivable that owing to our selection of these cases

because of their intractable epilepsy, they have come to operation several years before they would have produced symptoms of a space-occupying lesion. In other words, it is possible that had they not been removed at such an early stage, they might have later blossomed forth into more flagrant types of gliomatous neoplasm of more rapid growth and more eloquent symptomatology (Cavanagh, 1958; Cavanagh, Falconer, and Meyer, 1958).

In view of the marked improvement, both in epilepsy and in personality traits which have so consistently followed operation, we believe that these tumours in their respective cases must be regarded as the epileptogenic lesions. In the 2 cases of neoplasm which were benefited only 50 per cent as regards fit frequency (Cases HAR and EWA), the plane of excision skirted the edge of the tumour, and both probably were incompletely removed. It is interesting that in only 1 case (Case LIB) was Ammon's horn sclerosis present. Considering that Ammon's horn sclerosis so frequently dates from infancy and is often associated with a history of a difficult birth or infantile convulsions, it is noteworthy that in this particular case epilepsy had started at the age of 4 years. However, it was 1 of only 3 cases in this subgroup in which epilepsy had started before the age of 10 years. In none of our 13 cases of small neoplasms was there a history of difficult birth, infantile convulsions, or of major convulsions during the first decade of life.

B. Vascular malformations.—There were only 2 cases, the salient features of which are summarized on Table III. Both were women who

TABLE III.

CLINICO-PATHOLOGICAL CHARACTERISTICS OF VASCULAR MALFORMATIONS

PATIENT AGE, SEX	LESION	SITUATION	PRE-OPERATIVE CLINICAL FEATURES				POST-OPERATIVE FOLLOW-UP		
			Duration of Psychomotor Epilepsy (Yrs).	Plus Grand Mal	Personality	AIR-ENCEPHALOGRAMS	Duration (Yrs.)	Epilepsy	Personality
LEW 42, F	Capillary angeioma	Uncus	11	No	Paranoid	Normal	5	Fit-free	Improved
STE 40, F	Remnants of arteriovenous malformation	Fusiform and hippocampal gyrus	24	Yes	Paranoid	Slight dilatation of temporal horn	4	Fit-free	Improved

had suffered from psychomotor epilepsy for eleven and twenty-four years respectively. In the second case (Case STE) at another neurosurgical unit about two years previously a calcified lesion about 1½ cm. had been visualized radiologically in the inferior temporal gyrus, but it did not fill on carotid arteriography. It was then excised, being reported as a cirsoid angioma. None the less her fits and behaviour disorder

continued. After radical temporal lobectomy, however, her fits stopped and her behaviour improved. Examination of the specimen showed tiny remnants of angiomatous tissue in the fusiform and hippocampal gyri. As the patient had not been benefited by removal of the superficial calcified portion of the angioma, but only after the remaining deeper remnants had been removed, it is probable that these deeper remnants were responsible for the persisting epilepsy. We can also argue that in the first case (Case LEW) the tiny capillary angioma situated in the uncus, being the only lesion demonstrated, was also responsible for the epilepsy. Neither case exhibited sclerosis of Ammon's horn, and neither had a family history of epilepsy, or a history of difficult birth or infantile convulsions.

C. Cortical scars with or without other lesions.—There were 5 cases in this subgroup, the salient features of which are presented in Table IV. 3 cases with scars also had sclerosis of Ammon's horn, and the ages of onset of epilepsy in these 3 cases were 6 years, 8 years, and 18 years respectively (Cases MAR, GAM, and DAV). In only 1 case (Case DAV) was the scar visible to the naked eye. It was about 2 cm. in diameter, and had followed a small compound depressed fracture of the left temporal lobe at the age of 11 years. This was the only case which involved the overlying dura and which could be classified as a meningo-cortical cicatrix. In other cases the scars were only visible microscopically, and may have been incidental to the seizures. One of the cases (Case GAM), however, had an interesting and possibly relevant history. At the age of 8 years, she fell down some stairs but was not concussed. By the next day there was a marked change in her personality with outbursts of aggression, and four weeks later psychomotor fits began. She at no time had *grand mal*, and her birth had been normal—yet she also had mesial temporal lobe sclerosis.

The last case in Table IV is probably not one of anterior temporal lobe epilepsy. She was a girl with frequent psychomotor and *grand mal* seizures and with an aggressive personality, but she had a vigorously discharging focus, which on both electroencephalography and electrocorticography was entirely in the left posterior temporal region, outside the area of resection. The discharging area could not be removed owing to its proximity to the speech centres, but because the symptoms were very disabling she was submitted to a left anterior temporal lobectomy in the expectation that it would produce some amelioration. This however, has not been achieved, and she remains an institutionalized patient. With this exception, however, the therapeutic results in this subgroup of cases are encouraging. No etiological cause was apparent for the scattered cortical scars in Case CUN, whose fits had begun at the age of 45. He was a professional man of very high intelligence with

a normal blood pressure, but he did give a history of benign tertian malaria two years preceding the onset of symptoms.

We may perhaps summarize our consideration of this subgroup by repeating that in only 1 case (Case DAV) was there a history of certain post-natal head injury. In the case GAM there was a presumptive minor injury without local scalp damage or concussion. Similar minor head injuries were encountered in at least 5 cases in the subgroup of small neoplasms (Cases MAR, HAR, VAL, WOO, and MUN in Table II). Head injuries of such minor severity are common, and in these cases were probably incidental. In our experience of surgically treated temporal lobe epilepsy, therefore, cases of definite post-traumatic origin have been rare. This is somewhat at variance with the views of Gastaut (1954) who regards trauma as a common cause of temporal lobe epilepsy. It is, however, in keeping with the observations of Courville (1958) who points out that the mesial temporal structures are seldom damaged in cranial injuries, but that contra-coup lesions damage instead the inferior orbital surfaces as well as the dorsilateral and basal surfaces of the temporal lobes. It may well be that cranial trauma of the above type leads rather to bilateral than unilateral epilepsy and to generalized seizures rather than focal. It would seem as if our criteria of selection have excluded such cases.

D. Miscellaneous.—There remain 3 cases, which are summarized in Table V. All were epileptics of late onset. In 2 the underlying lesions were small cortical infarcts secondary to vascular disease (cerebral arteriosclerosis in 1 and chronic alcoholism in the other). Neither case was substantially benefited, although in the arteriosclerotic patient

TABLE IV.

CLINICO-PATHOLOGICAL CHARACTERISTICS OF CASES WITH CORTICAL SCARS

PATIENT AGE, SEX	LESION	SITUATION	PRE-OPERATIVE CLINICAL FEATURES			AIR-ENCEPHALOGRAMS	POST-OPERATIVE FOLLOW-UP		
			Duration of Psychomotor Epilepsy (Yrs).	Plus Grand Mal	Personality		Duration (Yrs.)	Epilepsy	Personality
DAV 27, M	Extensive scar at site of depressed fracture. Also Ammon's horn sclerosis	Inferior gyrus	9	Yes	Aggressive	Slight dilatation of left temporal horn	2	Fit-free	Improved
GAM 17, F	Small cortical scar. Also Ammon's horn sclerosis	Middle gyrus	9	No	Aggressive	Affected hemisphere slightly small with slight dilatation of temporal horn	3	Fit-free	Improved
MAR 29, M	- do -	Inferior gyrus	23	No	Normal	Affected hemisphere slightly small	2	Almost fit-free	Remaining normal
CUN 51, M	Multiple small scars	Fusiform gyrus and uncus	5	No	Neurotic	Moderate dilatation of contra-lateral temporal horn	2	Fit-free	Improved
HUN 17, F	Two small cortical scars	Middle and inferior gyri	16	Yes	Aggressive	Normal	3	Unchanged	Unchanged

TABLE V.

CLINICO-PATHOLOGICAL CHARACTERISTICS OF MISCELLANEOUS GROUP

PATIENT AGE, SEX	LESION	SITUATION	PRE-OPERATIVE CLINICAL FEATURES Duration of Psychomotor Epilepsy (Yrs).	Plus Grand Mal	Personality	AIR-ENCEPHALOGRAMS	POST-OPERATIVE FOLLOW-UP Duration (Yrs.)	Epilepsy	Personality
WOO 48, F	Cortical infarct due to arterio-sclerosis	Inferior and fusiform gyri	1	No	Hysterical	Slight displacement of affected temporal horn	4	Improved 50%	Unchanged
LAR 42, M	Scattered small cortical infarcts due to arterial degeneration ? alcoholism	Middle, inferior fusiform, and hippocampal gyri	4	Yes	Paranoid	Slight dilatation of temporal horn	1	Unchanged	Committed Suicide
LEP 46, M	Scattered mal-developed nerve cells (? tuberous sclerosis)	Fusiform and hippocampal gyri	3	No	Normal	Normal	3	Almost Fit-free	Remains Normal

(Case WOO) the fits have decreased by 50 per cent. Interestingly enough, in this particular patient the EEG examinations beforehand did not disclose any epileptic activity, and this therefore is the only case in our series in which the lateralization was primarily not an electrical one. Instead it was based upon a slight displacement of the left temporal horn as seen in an air encephalogram.

The last case (Case LEP) has scattered mal-developed cortical nerve cells of the type encountered in tuberous sclerosis, together with many grossly abnormal neuroglial cells in the white matter. Yet there is no family history, clinical, or radiological manifestation of this condition. This patient has been benefited by an anterior temporal lobectomy, and hence these abnormal nerve cells may have played a role in producing epilepsy.

RELATIONSHIP OF THESE LESIONS TO TEMPORAL LOBE EPILEPSY

It is reasonable to suppose that if a patient has been relieved of hitherto longstanding and intractable epilepsy by removal of cerebral tissue which subsequent examination shows to contain a focal lesion in an appropriate site, then that lesion was in some way responsible for the epilepsy. This is especially true if before operation the region of the resected tissue was the site of electroencephalographic epileptic disturbances.

If we apply these criteria to the various lesions which we have been considering, then it would seem likely that in their respective subgroups the neoplasms and their vascular malformations were the epileptogenic lesions, whereas this could not be said with any certainty for the scars and the miscellaneous lesions. Thus all the cases with neoplasm or vascular malformation were benefited. There were 15 cases in these

two subgroups, and 11 were rendered completely fit-free, 2 almost fit-free, and the remaining 2 improved almost 50 per cent as regards their epilepsy. It is likely that in these cases there were no other significant lesions in the rest of the brain, although the remote possibility of more than one tumour remains in a few of these cases. In those cases where benefit as regards fits was only partial the lesions were almost certainly incompletely removed. These results taken as a whole appear even better than the results of surgical removal of benign tumours which are associated with epilepsy. Thus Penfield and Erickson (1941) reported that 19 out of 29 patients with meningiomas, who had been adequately followed up, continued to exhibit epilepsy after operation. Again these same authors wrote that 9 out of 21 patients with meningiomas who had not had seizures pre-operatively, developed them postoperatively, generally within six months of operation. Such seizures, they thought, were due to scarring in the tumour-bed or in areas of brain injured during the approach to the neoplasm. The superiority of the results after temporal lobectomy in our small subgroup may be the consequence of our having removed the surrounding brain tissue as well as the neoplasm, and so interrupting neuronal circuits which were involved in the seizure-mechanisms.

When we come to the other two subgroups, our evidence that the pathological lesions present were the epileptogenic agents is uncertain. Thus, although 4 of the 5 cases with scars were benefited, in 3 of them sclerosis of the mesial temporal structures was also present, and this latter lesion might equally well have been responsible for the seizures. Furthermore, in only one of these cases with scar was there an unequivocal history of antecedent head injury. Again in the 3 cases of the miscellaneous subgroup, similar lesions to those removed may well be present in other parts of the brain, so accounting for the poor results of surgery in this subgroup.

Therefore in seeking to study further the relationship of the focal lesions to the mechanism of epilepsy, we shall confine our further analyses to the 13 cases of neoplasm and the 2 of vascular malformation. This makes a total of 15 cases, 8 of whom were males and 7 females. Their ages ranged from 2½ to 56 years, with an average age of 32 years. The duration of epilepsy before operation ranged from one to twenty-four years with an average of nine years, and an average age of onset of 23 years. All the cases suffered from psychomotor seizures, which had proved resistant to drugs, but only 3 of the 15 (20 per cent) had also suffered from *grand mal* seizures. In none of the cases was there a history of difficult birth or infantile convulsions forthcoming. These data contrast with our findings in earlier studies of cases with proved hippocampal-uncinate-amygdalar sclerosis (Cavanagh, Falconer, and Meyer, 1958) in that in these latter cases the average age of onset of epilepsy was 4½ years, there

was a history in more than 80 per cent (17 out of 21 cases) of difficult birth or infantile convulsions, while 13 out of the 21 cases (62 per cent) suffered from *grand mal* as well as psychomotor seizures. The natural history in this larger group therefore is clearly quite different from that of the group with focal lesions now under discussion. The same epileptogenic mechanisms may not operate in the two groups, especially as the anatomical disturbance in the temporal lobe is more restricted with the focal lesions and of a simpler order.

We shall now study our 15 selected cases of small focal lesions with regard to site of lesions, fit patterns, personality disturbances, and EEG findings.

Site of Lesions

In 8 cases the right temporal lobe was resected and in 7 cases the left temporal lobe (Table VI). Laterality to one or other temporal lobe,

TABLE VI.

SITES OF LESIONS

(NEOPLASMS AND VASCULAR ABNORMALITIES)

15 CASES - 7 LEFT-SIDED AND 8 RIGHT-SIDED RESECTIONS

	SITUATION IN TEMPORAL LOBE			LATERALITY OF CEREBRAL HEMISPHERES	
	Lateral Temporal Structures Only	Mixed Structures	Mesial Temporal Structures Only	Left	Right
NEOPLASMS (13)	3	5	4	5	8
VASCULAR MALFORMATIONS	0	0	2	2	0
TOTALS	3	5	6	7	8

therefore, is presumably not a factor in determining the onset of epilepsy. The histological nature of the individual lesions and their sites are given in Tables II and III. The listing of the individual sites given in these tables has probably a greater precision than is warranted on functional grounds, and therefore in Table VI we have divided the sites into 3 main groups, viz. those in which the lesions involve neuronal structures in only the lateral half of the temporal lobe (i.e. the middle temporal, inferior temporal and fusiform gyri), those in which the lesions involve neuronal structures in only the medial half of the temporal lobe (i.e. the hippocampal gyrus, uncus, hippocampus, and the amygdaloid complex), and a third group in which both halves were involved. In making this subdivision we realize that in several cases the lesion spreads into the white matter of both halves of the temporal lobe, and therefore we have postulated that from the epileptic viewpoint it is the neuronal

XUM

involvement which is the more important. This subdivision into lateral and medial halves has also the merit that it probably also conforms to differences in function of the two regions (Penfield, 1958).

On this basis in our 15 cases the epileptogenic lesion was primarily situated about equally in the lateral and medial temporal structures. We cannot tell from these particular figures therefore, whether involvement of the mesial temporal structures is more important for the production of epilepsy than is involvement of the lateral structures, as has been mentioned by Penfield (1956) and by Gastaut (1956). Certainly Case STE of the vascular malformations supports the view that involvement of the deeper structures is the more important factor. However, Feindel and Penfield (1954) have produced evidence to show that, although the initial epileptic discharges may come from any part of a temporal lobe, they do not produce the state of "automatism" (psychomotor confusion) until the discharges reach the periamygdalar region. They then project to deeper structures (Jasper and Rasmussen, 1958). There is thus generally a "march" in temporal lobe epilepsy comparable to that often seen in Jacksonian epilepsy (Stevens, 1957).

Fit-patterns and Their Relation to Site

All 15 cases showed attacks of psychomotor type,[1] whereas only 3 cases showed also *grand mal* (major convulsive) seizures (Table VII).

TABLE VII.

FIT PATTERNS IN 15 CASES OF FOCAL TEMPORAL LESIONS

	SITUATION IN TEMPORAL LOBE			LATERALITY OF CEREBRAL HEMISPHERES	
	Lateral Temporal Structures Only	Mixed Structures	Mesial Temporal Structures Only	Left	Right
PSYCHOMOTOR ATTACKS ONLY	4	4	4	6	6
PSYCHOMOTOR ATTACKS PLUS GRAND MAL	0	1	2	1	2

In this respect our series of cases differs markedly from the space-occupying tumours of its temporal lobe reviewed by Bingley (1958), whose cases showed psychomotor attacks in 31 per cent and *grand mal* in 75 per cent. It is interesting and perhaps significant that all 4 of our cases with lesions confined to the lateral temporal structures exhibited only psychomotor attacks. In some cases it is possible that *grand mal* convulsions were held in abeyance by medication, but this is only a

[1]Seizures characterized by sudden confusion with subsequent amnesia, and usually commencing with a remembered sensory aura. They are often accompanied by purposeful but poorly co-ordinated movements, but without a convulsion (Gibbs, Gibbs, and Fuster, 1948).

XUM

surmise. Certainly the low incidence of *grand mal* distinguishes the small focal lesions we are considering from cases of mesial temporal lobe sclerosis.

A rich variety of auras were encountered, and are listed in Tables VIII and IX. 1 case (Case SIN) had to be excluded from the compilation

TABLE VIII.

VARIETIES OF AURA OCCURRING IN 14 CASES OF FOCAL TEMPORAL LESIONS

SOMATIC SENSATIONS		
Epigastric and/or abdominal (including 2 cases with genital sensations)	5	11
Epigastric rising to throat	4	
Cephalic	2	
PERCEPTUAL ILLUSIONS		
Déjà vu	3	8
Strangeness or unfamiliarity	3	
Micropsia	2	
TASTE AND/OR SMELL		7
VISUAL HALLUCINATIONS (organised and unorganised)		3
FEAR		2
TINNITUS		2
TOTAL AURAS ENCOUNTERED:		33

TABLE IX.

CORRELATION OF AURAS WITH SITES OF LESIONS

	SITUATION IN TEMPORAL LOBE			LATERALITY OF CEREBRAL HEMISPHERES	
	Lateral Temporal Structures	Mixed Structures	Mesial Temporal Structures	Left	Right
SOMATIC SENSATIONS	1	4	6	4	9
PERCEPTUAL ILLUSIONS	2	4	2	2	6
TASTE AND/OR SMELL	0	4	3	2	5
VISUAL HALLUCINATIONS	0	2	1	1	2
FEAR	0	1	1	0	2
TINNITUS	1	0	1	2	0

because of its youth, but in the remaining 14 cases some 33 different auras were encountered, multiple auras being described in all but 1 case. All the auras recorded have been reported as commonplace with temporal lobe lesions (Penfield and Kristiansen, 1951; Falconer, 1954). It is,

XUM

however, interesting although probably not significant in view of the small numbers, that such auras as vertigo, reminiscence, or panoramic memory were not represented.

The most frequent auras were various somatic sensations (11 instances) of which epigastric or abdominal sensations (9 instances) were the most common. In fact somatic sensations were present in 10 of the 14 cases listed in Tables VIII and IX. It is interesting that testicular and penile sensations occurred together with an abdominal feeling in 2 cases; such a combination of sensations has been described by Penfield and Kristiansen (1951).

Next in frequency come perceptual illusions (8 instances) followed by auras of taste and/or smell (7 instances). Except in 1 patient (Case EWA) where a taste sensation occurred as a solitary aura, these olfactory and gustatory sensations were usually preceded by one of the other auras. Finally visual hallucinations occurred in 3 patients, while fear and tinnitus each occurred in 2 patients.

A comparison was then made of the varieties of auras with the sites of lesions (Table IX), and this showed what are possibly some significant correlations. There does not appear to be any significant correlation in the incidence of perceptual illusions, of fear, or of tinnitus. There is, however, a striking correlation with regard to taste and/or smell, for in all instances the lesion was involving the mesial temporal structures. A closer scrutiny of sites showed that in 5 of these 7 cases the lesion was centred in the amygdala, while in the remaining 2 it was situated in close proximity in the adjacent uncus and anterior part of the hippocampal gyrus. All these lesions, therefore, were in direct relation to what are now accepted as secondary olfactory areas (Le Gros Clark and Meyer, 1947; Allison, 1954).

There is a possible correlation between site and somatic sensation for in 10 out of the 11 instances the lesions were also situated mainly in the mesial temporal structures. The exception was a case in which a cephalic sensation was the aura (Case VAL in Table II). It is well known to clinicians that cephalic sensations are often described by patients in vague terms, and certainly this was true of the particular patient concerned. It may, therefore, be of significance that in all instances of epigastric or genital sensations the lesions concerned were in the medial temporal structures. Relevant to this are the observations of Jasper and Rasmussen (1958) on electrical stimulation of various parts of the temporal lobe for they elicited similar responses only from the deeper parts of the lobe. Finally, we have the 3 cases of visual hallucinations, and all 3 were in the mesial temporal region; but the cases are too few for any definite conclusions to be drawn.

Lastly an attempt was made to correlate the varieties of aura with the laterality of the resected temporal lobe. As with the incidence of epilepsy

XUM

there were no definite correlations. In view of Penfield's recent statement (1957 and 1958) that in his experience visual illusions and auras of déjà vu have come predominantly from the minor cerebral hemisphere, it is interesting that in both our cases of micropsia the lesion was in the right hemisphere. However one case of déjà vu had a lesion of the dominant temporal lobe. One of the 3 cases with visual hallucinations likewise had a lesion of the left or dominant temporal lobe.

Personality Disturbances

Many authors have stressed the frequency with which personality disturbances are associated with temporal lobe lesions (Hill *et al.*, 1957) and the extensive literature on this subject has recently been reviewed by Bingley (1958). It is therefore not surprising that personality disorders of various kinds were encountered in 12 of our 15 patients with small tumours or angiomas, especially as 9 of these patients were referred from psychiatric sources, and only 6 from general hospitals or neurological clinics.

The range and frequency of the personality disturbances encountered are set out in Table X, each patient being given only one listing according

TABLE X.

PERSONALITY DISTURBANCES NOTED IN 15 CASES OF SMALL FOCAL TEMPORAL LESIONS

NORMAL PERSONALITY	3 Cases
AGGRESSIVE OUTBURSTS	4 "
INADEQUATE INEFFECTUAL PERSONALITY	2 "
PARANOID AGGRESSIVE STATES	2 "
HYSTERICAL PERSONALITIES	2 "
DEPRESSIVE REACTIONS	1 "
DEFECTIVE ANTI-SOCIAL BEHAVIOUR	1 "
	15 "

to the single predominant abnormal feature as defined in a previous communication (Falconer *et al.*, 1958). As the lesions were all small, in none was there a factor of raised intracranial pressure, and hence the torpor which has been remarked upon so commonly by various authors in cases of temporal lobe tumours was completely missing in our patients (Bingley, 1958). Nor in the inter-ictal periods was there any overt neurological deficit, such as a dysphasia or visual field disturbance.

Only 3 patients were judged to have a normal personality pre-operatively.

XUM

As with cases of temporal lobe epilepsy due to mesial temporal lobe sclerosis (Falconer *et al.*, 1958) outbursts of aggressive behaviour were the most frequent abnormality encountered, and likewise was the abnormality which responded most readily to operation. This type of abnormality tends to be explosive and seems to be more directly related to the occurrence of fits than are the other disturbances (Falconer *et al.*, 1958). However, even the other personality disturbances were improved in varying degree following operation, probably because the epilepsy was also improved. Even the 2 patients with inadequate ineffectual personalities were able to resume work, while the feeble-minded youth lost his antisocial attitudes.

The intelligence quotients of our various patients (Table XI) tended

TABLE XI.

INTELLIGENCE RATINGS IN 15 CASES OF SMALL FOCAL LESIONS

INTELLIGENCE QUOTIENTS	
Below Average	3
Average 90 - 110	4
Above Average	6
NOT TESTED	2

to be above average, the highest rating being 135 (Case MUN in Table II). This contrasts with previous observations in cases of mesial temporal lobe sclerosis where the intelligence scores tend to scatter in the opposite direction (Falconer *et al.*, 1958). In no case was the intelligence quotient significantly altered by the subsequent temporal lobectomy, although all cases in which a left-sided (i.e. dominant) temporal lobectomy was performed subsequently showed impairment of learning in respect of auditory modalities, as described by our colleagues Meyer and Yates (1955). The laterality of the lesion to either the left or the right temporal lobe did not seem to influence the intelligence quotients recorded in our patients.

Our cases are too few to permit us to make statistically valid deductions with regard to the kinds of personality change, but they may illustrate a trend. Thus when the presence or absence of personality changes are compared with the sites of the lesions, it is noteworthy that all 3 cases with normal personality (Cases MAR, VAL, and WOO in Table II) had lesions limited to the lateral half of the temporal lobe. Incidentally all three involved the dominant temporal lobe which is also noteworthy in view of Bingley's (1958) conclusion that mental symptoms are more common with lesions of the dominant than of the non-dominant temporal

lobe. In the only other case in the series in which the lesion was confined to the lateral half of the lobe (Case SIN in Table II) the patient was a child and there were aggressive features. All 9 of the remaining cases of neoplasm and angioma had lesions extending into or involving primarily the mesial temporal structures, and all had personality disturbances. These findings may possibly link up with the observations of Kaada *et al.* (1953 and 1954), of Green (1958), and of others that behavioural disturbances can occur in animals following unilateral experimental injury or electrical stimulation of the amygdalar or hippocampal regions. It must be remembered however that such experimental lesions do not necessarily lead to abnormality, and that some patients with epilepsy occurring in association with Ammon's horn sclerosis retain a normal personality (Falconer *et al.*, 1958).

Electroencephalographic Findings

This aspect of the focal lesions has recently been considered by our colleagues, Kennedy and Hill (1958) but in a wider group of cases. They have shown that the routine use of sphenoidal needle electrodes combined with barbiturate-induced narcosis provide EEG data that are often of predictive value in determining the sites in the temporal lobe of maximal pathological change, although by themselves they can only sometimes predict the nature of that change. We have little to add further to what they have already pointed out, and we are grateful to Dr. W. A. Kennedy for supplying us with data relative to our present cases (Table XII).

TABLE XII.

CORRELATION OF E.E.G. DATA WITH SITES OF FOCAL LESIONS (IN 15 CASES)

SITUATION OF LESION	MESIAL TEMPORAL STRUCTURES ONLY (6 PATIENTS)	MIXED STRUCTURES (5 PATIENTS)	LATERAL TEMPORAL STRUCTURES ONLY (4 PATIENTS)	TOTALS
Ipsilateral spike-discharging focus:				
Predominant over lateral temporal surface	2	2	? 1	5
Predominant at sphenoidal electrode	4	3	2	9
Independent spike focus in opposite temporal lobe	3	2	0	5
Associated slow-wave activity	6	5	2	13
Reduced barbiturate-fast activity at ipsilateral sphenoidal-ear electrodes	4	1	0	5

XUM

In all but 1 of the 15 cases which we are now studying there was a spike-discharging focus within the affected temporal lobe, usually predominantly located at the sphenoidal electrode (9 instances) but sometimes predominant over the mid-temporal convexity (5 cases) when it also usually spread to the inferior temporal region. The frequency of these spike discharges varied greatly, and in 5 cases they were found to be potentiated by barbiturate narcosis (Pentothal or Seconal), while in 3 cases they were diminished. In only one case did the spike discharges spread directly to the opposite hemisphere.

Scrutiny of our cases gave us no clue as to why in some cases the predominant focus was located at the sphenoidal electrode and in another case at the mid-temporal electrode (*see* Table X). Even in cases with the same type of tumour in the same region of the temporal lobe (e.g. cases MUN and STA in Table II) the discharges could be predominant at either site.

In 5 cases, however, there was an independent but subsidiary focus of spike discharges picked up by the sphenoidal electrode beneath the opposite temporal lobe. This phenomenon of a unilateral lesion producing bilateral spike discharges has been observed both in patients and experimental animals by several observers (Ajmone-Marsan and Stoll, 1951; Gastaut, 1954; Penfield and Jasper, 1954; Kennedy and Hill, 1958). It is interesting that in all our 5 patients this independent focus in the opposite temporal lobe disappeared after operation, the EEGs ceased to show any epileptic activity, and the patients became fit-free. Presumably in none of these cases was there a second tumour or angioma in the other cerebral hemisphere.

Diminution of barbiturate-fast activity between the sphenoidal and ear electrodes was observed in 5 of our 15 cases. All were cases in which the mesial temporal regions were principally involved. Kennedy and Hill (1958) have pointed out that this finding has a very high correlation with the presence of marked changes in the mesial temporal structures, and occurs with especial frequency in cases of well-marked sclerosis of those structures. However, its presence, although indicative of pathological change, cannot be used by itself to determine the nature of that change.

In only 1 of our cases was no epileptic activity detected on repeated EEG examinations. This was the case of cholesteatoma indenting the middle temporal gyrus (Case WOO). In this particular case diminished barbiturate activity was observed between the sphenoidal and ear electrodes, while some irregular slow-wave activity at 4 to 7 c.p.s. was also observed in the middle and posterior temporal regions. Mild to moderate degrees of slow-wave activity were also observed in the affected temporal lobe in 12 of the remaining 14 cases which we are now studying. However, similar slow-wave activity has occurred in some of our cases

XUM

in which mesial temporal lobe sclerosis was found. All we can say, therefore, is that while slow-wave activity in the temporal region is not usually of differential diagnostic value, its absence pre-operatively makes a focal lesion unlikely.

Post-operatively epileptic activity disappeared from the records of 12 of our 15 patients, while some spike activity was still observed at periods of up to two and a half years in the remaining 3 patients. This improvement in the EEG records parallels the improvement in the clinical status, although it does not absolutely coincide with it.

Summary and Conclusions

It may well be that our criteria for selecting patients for operation (Falconer *et al.*, 1955) have influenced the spectrum of cases described in this report. The paucity of cases with definite post-traumatic origin has been remarked upon, and appears to be in contrast with the experiences of Gastaut (1954 and 1956). Again all our patients exhibited psychomotor types of epilepsy (with in addition in some instances *grand mal* or mere absences). In contrast Bingley (1958) reports that in a large series of epilepsy associated with known temporal lobe lesions or with EEG evidence of temporal lobe discharges, psychomotor seizures occurred in 78 per cent of his non-tumour cases, but only in 31 per cent of his cases with tumours. His tumours, however, were space-occupying lesions and consequently may have exerted effects beyond the temporal lobes.

The various lesions which we have considered were disclosed as a result of our policy of removing the affected temporal lobe in one piece and of subsequently submitting it to detailed histological examination. So far we are unaware of any previous clinico-pathological study of them. Despite the relatively small numbers of cases at present available for analysis it is clear that certain important trends can be made out, both of a positive and of a negative character. These may ultimately come to throw light on the mechanisms concerned in producing temporal lobe epilepsy.

Of the four classes of process encountered in this study by far the most important are the neoplasms and the vascular malformations. They are quite common, for together they account for about 1 in 5 of the cases of temporal lobe epilepsy which we submit to operation, without unequivocal radiographic evidence of a space-occupying lesion. In general they are small lesions, relatively well-circumscribed and of an indolent nature. Both the medial and lateral regions of the temporal lobe may be affected, and where the former are involved the amygdaloid complex is probably the most critical site. As regards fit patterns those cases with laterally placed lesions would appear to be less prone to exhibit *grand mal*. On the other hand disturbances of smell and/or taste are found only with medially lying lesions affecting predominantly

XUM

the amygdaloid complex and adjacent rhinencephalic sensations. A similar relationship seems likely for cases with somatic sensations. Psychomotor and *grand mal* seizures appear to occur independently of whether the lesion is in the right or the left temporal lobe.

Unfortunately it has not been possible to draw any important conclusions from the group showing cortical scars or from the miscellaneous group. The number of cases is too small. Moreover, the cortical scars with two exceptions are complicated by the association with Ammon's horn sclerosis, the position of which in relation to psychomotor seizures is still debatable (Cavanagh, Falconer, and Meyer, 1958). Furthermore the presence of other changes outside the temporal lobe cannot with certainty be excluded. It is however perhaps surprising that epilepsy with a definite post-traumatic origin has not been more frequent in our case-material which contains only one certain example.

Probably the most important practical finding is the high improvement rate that would appear to follow radical lobectomy for focal lesions, provided that additional changes outside the temporal lobe can be reasonably excluded. However, the criteria by which such cases can be selected for operation are still imprecise. In this particular study we have excluded cases in which the neuroradiological studies showed clear evidence of a space-occupying lesion, and have concentrated upon the intractability of the epilepsy to drug therapy and the electroencephalographic evidence of a discharging epileptic focus predominant in one temporal lobe. In all these respects, however, a longer experience is required, and our criteria for selection of cases may well change or expand.

Lastly one must remember that the lesions which we have been considering, although important, are but one of the factors which can cause epilepsy. Reminders of this have recently been given by Crome (1955) and by Haymaker and his colleagues (1958), who have reported cases of lesions comparable to those which we have described but occurring without epilepsy. This has of course long been known. It would appear that for the production of epilepsy there must be in addition to a lesion which acts as an epileptogenic trigger some generalized or constitutional factor the nature of which is unknown, but may be biochemical.

Acknowledgments

All our cases were studied electrographically before and after operation by members of the Department of Clinical Neurophysiology of the Institute of Psychiatry under the direction of Dr. Denis Hill, while half of them were actually referred for surgery from his wards. This study would not have been possible without his active collaboration for which we are grateful. We also wish to thank Professor A. Meyer, who initiated and stimulated the pathological studies, Professor P. Daniel

XUM

who supplied us with facilities for these studies, Dr. R. Hoare for neuroradiological studies, and Sir Charles Symonds, who referred to us several of the remaining cases, for his kindly criticisms in the preparation of this paper. We are also indebted to the Medical Research Council for the assistance of Dr. J. L. Wilson and Dr. I. P. James, who have supplied us with much of the clinical and follow-up data.

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A STUDY OF THE PSYCHOLOGICAL FACTORS IN A CASE OF SENSORY REFLEX EPILEPSY[1]

(PSYCHOLOGICAL FACTORS IN REFLEX EPILEPSY)

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INTRODUCTION

HUGHLINGS JACKSON directed attention to reflex epilepsy by his description of a case in 1886. It appeared to him that such patients offered an opportunity for studying some of the immediate external causes of convulsions. The seizure consisted of a sudden collapse in which the patient turned red, looked vacant, respiration stopped and the eyes turned upward and to the right in parallel. They were provoked by touching any part of either side of the head or face but unless the patient was taken unawares the tactile stimulus was ineffective. What at first sight had appeared to be a simple stimulus-response mechanism turned out on closer study to be much more complex. Critchley (1933) emphasized the multiplicity of factors operating in "reflex" epilepsy and Wilson (1940) pointed out that a classification of such seizures according to the provoking stimulus was unsatisfactory. In cases similar to the one described by Jackson, Critchley supposes that the fit is a response to a successfully evoked "startle" reflex, the latter being evoked by an auditory or tactile stimulus. Critchley (1937), Shaw and Hill (1947) Daly and Barry (1957) and others discuss cases of musicogenic epilepsy where often the fit appears to be a response to the effect associated with the music. Matters were further complicated, before the development of electroencephalography, by the difficulty sometimes of distinguishing true epilepsy from hysterical manifestations. When there is a definite EEG change in response to a stimulus, this distinction is easier to make and the opportunity presents of studying the electrical changes of ictal responses to complex affective changes, Shaw and Hill (1947), Mitchell, Falconer and Hill (1954). In the ideal case the observer can control the conditions for observing the evocation of a fit.

[1]Supported by a grant from the Ford Foundation.

XUM

The following is a description of some psychological and electroencephalographic investigations carried out on a patient suffering from a form of reflex epilepsy. This case was under the care of Mr. Murray Falconer who kindly made the patient available for these studies.

Case Report

The patient was an intelligent boy (I.Q.130) of 18 years. The father and mother are alive and well. The mother had a cousin who suffered from occasional blackouts but apart from this relative there was no family history of cerebral disease, psychiatric or neurological illness. The pregnancy and birth were uneventful. There were no neurotic symptoms in childhood apart from occasional enuresis until the age of 6 years and a slight stammer when he first talked. He had chickenpox and whooping cough at the age of 2, measles when 5 and mumps at the age of 7. None of these illnesses were considered serious but during mumps the patient fainted twice. He never suffered a severe head injury with loss of consciousness. He was an above average pupil and made a good social adjustment at the grammar school which he left at 16. After leaving school he became a clerk and passed two promotion examinations but unexpectedly failed a third. He was a cheerful, active, popular boy with a steady girl friend who was sympathetic about his fits. No psychiatric abnormalities were revealed on examination other than some obsessional traits (he tended to be over-meticulous and orderly). He was a thick-set, muscular individual, right handed, and with no abnormal physical signs in the central nervous system and in particular no evidence of parietal cortical deficit. The X-ray of the skull was reported (Dr. R. Hoare) as showing a scaphocephalic type of craniosynostosis, and in addition the sagittal suture had closed prematurely. The calcified pineal body lay in the mid-line and the right choroid plexus was calcified. The lumbar pneumoencephalogram appeared within normal limits. A left carotid arteriogram was performed at the Bristol Royal Infirmary and revealed no abnormality. A series of electroencephalographic investigations demonstrated a localized focus of spike activity in the left parietal region and subsequently at operation a vascular lesion was removed. This was shown to be an angioma, the histological report (Dr. Sabena J. Strich) being as follows:

> "The white matter and cortex appeared normal and sections showed a tangle of blood vessels of all sizes including a large artery and vein. Many vessels showed fibrosis of the adventitia and there was gliotic brain substance between the vessels. The lesion was thought to be an angiomatous malformation."

According to the mother the illness began at about the age of 7 years with a complaint of a "funny" feeling in the right arm for half a minute once or twice a month, often following when she washed the right side of his face with the flannel. The patient verified this, describing the feeling as "tingling" and like "a limb coming back to life after being in an awkward position." He could bring on the sensation quite rapidly by rubbing the right side of his face. The mother reported that major convulsive seizures, which occurred about once a week during his sleep, began at the age of 14. He was given phenobarbitone a month later and subsequently had only one such attack two years afterwards when the drug was temporarily withdrawn. Over the three to four years before his admission to the Neurosurgical Unit the sensory fits had changed in character and had become associated with a tonic abduction of the right arm. For the last six months they had occurred three to four times daily and in addition he often fell during an attack. The patient described two types of spontaneous attack, one with no warning and one commencing with an aura of a throbbing, pulsating unpleasant sensation occurring simultaneously in the right side of his face and the whole of the right upper limb. Observation showed that after five to fifteen seconds the whole body, including the muscles of the chest wall, stiffened. The right

arm, elbow flexed to a right-angle, was slowly abducted at the shoulder to over 90 degrees and at the same time the head turned to the left although the eyes were turned to the right. Some two to three seconds later the extended left arm was abducted to about 45 degrees. This posture was terminated after twenty to thirty seconds by a brief phase of mild clonus. Though the patient did not lose consciousness he was unable to speak. During the attack and for a short time after he had no awareness of the right arm and did not know where it was in space. This characteristic motor pattern also occurred on the few occasions when he had attacks from which the aura was completely absent. He considered that these attacks most frequently occurred when he felt himself in an awkward situation.

In addition to the spontaneous attacks he induced others by rubbing the skin of the right side of his face. The patient found that he was having an average of three fits a day and to prevent their occurrence at socially inconvenient times he would precipitate them at home. This manœuvre was performed by rubbing the back of the fingers of the left hand with increasing vigour over the right cheek with strokes extending from the right mandible to just above the right zygomatic process. His eyes would appear blank or would be closed. His rubbing (when it induced a fit) appeared to him to get into step with the throbbing aura sensation, this became intense and the fit would commence with a faltering in the rhythm of rubbing which ceased as the arm went up in the attack. The pattern already described would then develop. Chance contact, for example shaving, might also provoke a fit. Whilst in bed at night he would frequently rub his face on the pillow or with his hand to produce a faint aura sensation or rather more vigorously to produce a full aura but stopping before a fit occurred.

METHOD

Prior to the detailed study of this case, routine EEG records were obtained; these included six on a 16-channel apparatus and four on an 8-channel. During these investigations the characteristic form of the index (as defined below) was recognized and its relation to the stimulus established. It was observed too that it occurred at times independently of the stimulus. In addition the focal nature of the discharge and its location in the left parietal areas was established. Three of the records were continuous over a period of eight hours on each of three separate days. The experiments which are the subject of this communication were performed on five further days. An electrocorticogram also was recorded at operation. The EEG was therefore recorded during a total period of approximately forty-two hours pre-operatively and fourteen hours post-operatively. During two sessions a period of photic stimulation was given and one record was taken with sphenoidal wire electrodes in position. Oral glucose, intravenous thiopentone ("pentothal"), Bemegride ("megamide") and Leptazole ("metrazol") were used, the latter two in order to induce a fit during clinical and electrographic observation. On other occasions tape recordings of interviews were made and co-ordinated with the EEG by means of an electrical marking system. These sessions were planned to include periods of silence, light sleep, conversation and tasks, as described below. The patient signalled the experience of the aura by pressing an EEG marker button.

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A. *Experiments in Normal Waking State*

(1) Throughout two sessions the patient was instructed at fifteen-minute intervals to rub his face for fifteen seconds, and throughout a third session to do so at ten-minute intervals. He was otherwise resting, reading, eating or talking. During one session the interval between the instruction "Get ready to rub" and "start rubbing" was kept constant for six rubs. This interval was then suddenly extended without warning to twice the usual length, for the next three trials.

(2) The patient was asked to imagine rubbing his face in his customary manner but not to do so.

(3) He was engaged in conversation in an interview situation.

During experiments 2 and 3, one of us (L. G.) sat beside the patient who lay on a couch separated from the instrument room by a wall with a communicating hatch.

B. *Experiments with the Patient Hypnotized*

The hypnotic state was produced without adhering to any ritual. This has been described elsewhere, Goldie (1956, 1959) and was introduced to increase the control of the stimulus situation. In this state the patient was told that on a signal (a count of three) he would find himself experiencing, for example, rubbing his face. The appropriate instruction was added, e.g. "You may move your arm but not touch your face", or "You will remain absolutely still." The aim was to produce a hallucination in what is supposed to be a highly suggestible state, i.e. the hypnotic state.

(1) He was briefly touched by the hypnotist (L. G.) on the left cheek, then left brow, right brow and right cheek, following the suggestion of anæsthesia of the right cheek.

(2) He was told to make his usual rubbing movements but without touching his face, experiencing this as actual rubbing.

(3) He was told to rub his left hand with his right and vice versa without any suggestion as to effects.

(4) He discussed certain topics with the hypnotist.

(5) He was asked to imagine rubbing his face during the recording of an electrocorticogram at operation under local anæsthesia. It was not possible to be certain that the patient was in fact hypnotized during this procedure.

The EEG response, discussed below in more detail, was a characteristic burst of spike activity that was distinctive in form, character, location and temporal sequence (fig. 1). Hereafter it will be referred to as the "index" since it has this characteristic form. The records were scrutinized and clear unequivocal episodes of this spiking activity marked throughout. The tape records were then correlated with the EEG and the circumstances associated with the appearance of the index were noted.

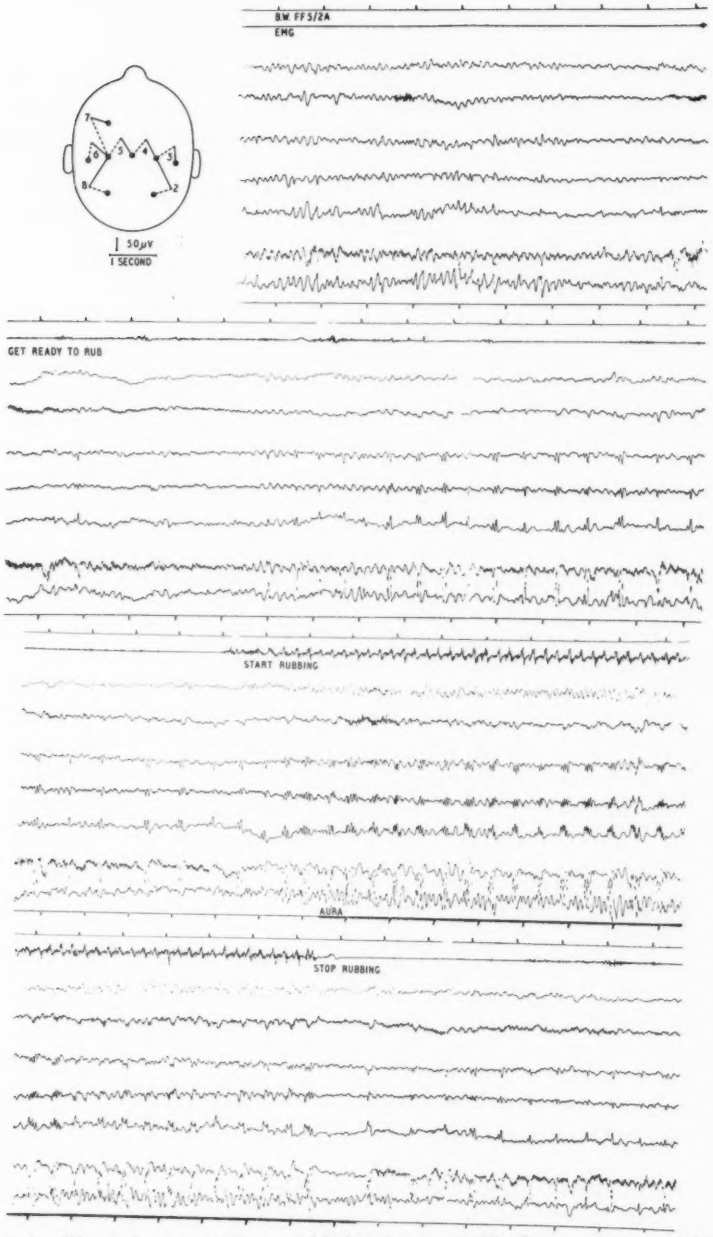

FIG. 1.—The patient was told to rub his face (*see* text). The four sections reproduced here are a continuous record. The EMG was recorded from the left wrist. The patient pressed a button when he had the aura and this is shown as a thick line on the bottom time-marker. The illustration shows the characteristic bursts of spike activity referred to as the index when the patient rubbed his face and also that these follow the instruction "get ready to rub," before actual rubbing of the face occurs.

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Preliminary EEG investigations had shown that a focus of inter-seizure spike potentials was present to the left of the mid-line in the parietal area. During the investigations described special recording arrangements were used, the relation of the electrodes to the focal area being as shown in the illustrations. The amplifier sensitivity was 7 mm. for 50 μV input and the time constant was 0·3 seconds for the routine records and 0·1 second for the experimental records in order to reduce movement artefact and to maintain direct comparisons during the experimental sessions.

Results

Routine recordings using different techniques have been noted above. Details of these are not discussed as they contained little of relevance to the main object of this study. The patient was told to rub the right side of his face with his left hand on 88 occasions (this total excludes those occurring in the ten minutes immediately following a fit). The interval between rubs were kept constant on each day by means of a stop watch. This stimulus was followed by the index on 48 occasions (fig. 1), and no change occurred on 40 occasions (Table II). The effectiveness of the reflex stimulus was observed to be extremely variable from day to day. Moreover, the time relation between stimulus and appearance of the index was itself a variable. Thus on trial-day 4, 40 stimulus occasions resulted in only 9 discharges, while on trial-day 5, which was nineteen days later, 32 stimulus occasions resulted in the appearance of the index 31 times.

The sequence of events relating to the index was as follows. When spiking appeared it was usually after the commencement of rubbing, but there were seven occasions when spiking preceded this act, at a time when the hand was poised to commence rubbing (figs. 1 and 5). When spiking followed the start of the rub stimulus, it did so at a variable time afterwards but most frequently after 3–7 seconds. The spikes in the discharge varied and often continued beyond the period of rubbing (24 occasions), sometimes for as long as 10–15 seconds. The patient reported the aura on occasions when there was no spiking, and at other times the aura occurred in an irregular association with rubbing and with spiking. However, if a clinical seizure eventuated in response to rubbing, the patient experienced the aura, although the electrical pattern was not consistent. Indeed the characteristic form of the spiking index was sometimes less apparent on the occasions when the rub-stimulus provoked a clinical seizure. The aura therefore had no consistent relationship to spiking activity as recorded by the EEG.

When a clinical seizure occurred it was followed by a refractory period of 7½–9 minutes when no spikes of any sort were seen in the resting EEG record and none could be evoked by any physical or psychological procedure. On one day after a clinical seizure, spiking activity was

elicited by rubbing after this refractory period and the size and duration of the discharges increased progressively until a further clinical fit resulted. This cycle could not be reproduced on two further occasions. There was no gross cycle of excitability evident on making a close study of the fit frequency over a period of three months. It may be noted that during days of infrequent fits psychological stimuli were more effective than actual rubbing of the face in producing spiking activity (the index).

Circumstances Associated with the Appearance of the Index

In order to assess the frequency of spontaneous occurrence of the index during the resting state a sample of recordings (totalling 15 hours 35 minutes), which had been taken before the psychological experiments, was examined (Table I). This sample was a series of mostly consecutive

TABLE I

	Numbers of episodes in 15 hours 35 minutes of routine recording time	
A. "*Spontaneous*" Unrelated to any known external stimulus noted on record	10	
B. "*Spontaneous*" Related to noted external stimuli		50
Reading	10	
Micturition	4	
In relation to eating	5	40
Fidgeting	9	
People going into room	9	
Footsteps, voices, blind pulled down	3	
	Number of episodes in 3 hours 28 minutes of experimental recording time	
C. Index related to known psychological stimuli, Day 1 and 2	35	

A and B occurred during 15 hours 35 minutes of routine recordings in the resting state.

routine records taken by different recordists in the main hospital laboratory. The patient's behaviour and external events were marked on the record by the recordists. It should be noted that in this large laboratory many things are taking place, for example people coming and going in the main room, the telephone ringing, conversation etc. Despite the difficulty of assessing the significance of all these external events Table I shows that during the long period of 15 hours 35 minutes recording, the index appeared on only 10 occasions unrelated to any known stimulus, and on 40 occasions temporally related to known stimuli. Moreover, during a

XUM

much shorter period of 3 hours 28 minutes recording, under experimental conditions, the index appeared on 35 occasions in relation to known psychological stimuli. The results shown in Table I were treated statistically and for this purpose A and B were added together making a total of 50 appearances of the index in 15 hours 35 minutes. This was compared with C in which 35 appearances of the index occurred in 3 hours 28 minutes. If two equal periods of time (3 hours 28 minutes) are considered, we observe (approximately) 11 episodes in one situation (A+B) and 35 episodes in the other situation (C), a total of 46. On the nul hypothesis that the situations do not differ we would expect 23 episodes in each situation. On testing the observed against the expected using a Chi square test we obtain a value of $\chi^2 = 12{\cdot}52$ which with 1 degree of freedom is significant with probability $P \leqslant 0{\cdot}001$. Hence we must reject the nul hypothesis for the evidence is strong that the two situations are different. In other words, the possibility of 35 indexes occurring in one situation as against 11 in the other far exceeds anything which could occur by chance alone.

A. *Experiments in the Normal Waking State*

(1) During a recording in the normal waking state, at fifteen minute intervals the patient was instructed to rub his face for fifteen seconds and on six consecutive trials the interval between the instruction "Get ready to rub" and "Start rubbing" was kept constant at nine seconds. On three further trials this interval was extended without warning to twice the usual length, i.e. to eighteen seconds. On each of these occasions the index in the EEG appeared at approximately six seconds after the instruction "get ready to rub," whilst the patient was still immobile and prior to him actually rubbing his face (figs. 1 and 5).

(2) In the early experiments the EEG was unchanged when the patient attempted to imagine, as vividly as possible in the normal waking state, rubbing his face in his usual fashion.

(3) The patient was engaged in conversation (described in detail below with topics discussed under hypnosis).

B. *Experiments with the Patient Hypnotized*

The patient was hypnotized thus producing greater control of the "stimulus" situation.

(1) In this state it was suggested that the right side of his face would become anæsthetic (the actual suggestion was that the right cheek would become "frozen and insensitive"), and then the patient was briefly touched on the left cheek, left brow, right brow, and right cheek in that order. Slight spiking occurred to all except the last touch which was associated with the appearance of the index for forty-four seconds; later the patient spontaneously reported that his face had "gone cold" but that he still felt

XUM

touch. Thus the patient's interpretation of the suggestion was not the one intended. Instead of anæsthesia and unawareness his attention was in fact focused on the right side of the face.

(2) The hypnotized patient was told on a signal to make the usual rubbing movement some three inches from the face and to experience this as actual rubbing (figs. 2A and 2B). The index was obtained on twelve

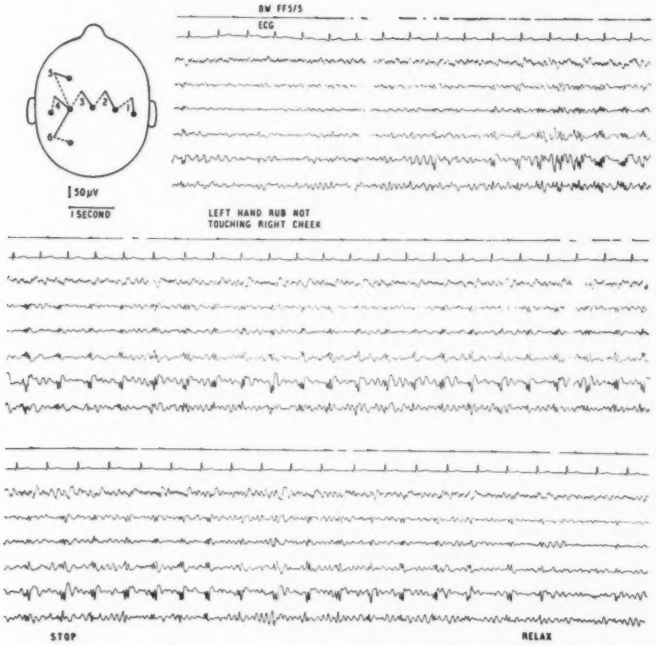

FIG. 2.—*Hallucinated rubbing—patient hypnotized.*—The index appeared as the patient went through the motions of rubbing his face without contact. When he did touch his face (B) there was no increase in spiking. The two examples, A and B, are themselves continuous but taken on different days. The arrangement of channels is the same in each case. The ECG was recorded from both wrists. 2A above.

out of seventeen trials as shown in Table III. It is of interest to note that on one occasion of hallucinated rubbing the patient went into a fit, momentarily touching his face as it began. The detail of the data in Table III is given to illustrate that the responses showed a random occurrence and did not apparently reflect any obvious cycle of excitability or conditioning process. The results of Table II and Table III were treated statistically. Here we have two situations. In the first, the patient actually rubs his face on 88 occasions and the index appears on 48 of these and in the second, it

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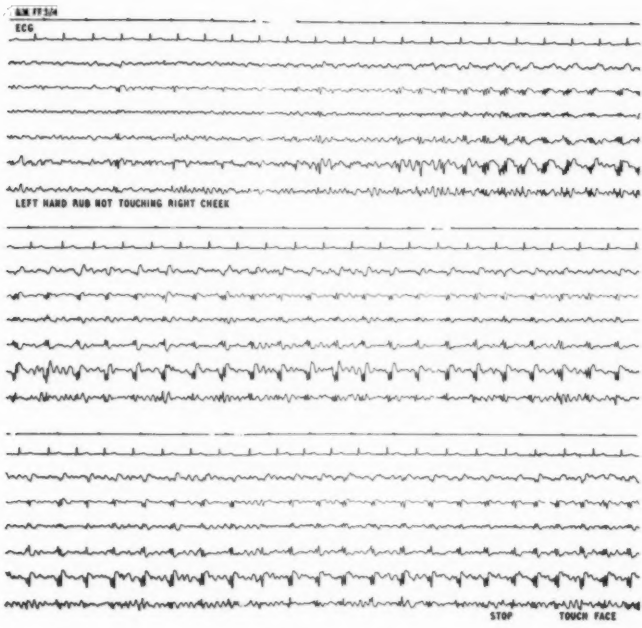

FIG. 2B *(see previous page)*.

TABLE II.—STIMULUS-INDEX RELATIONSHIP

	Trial day		*Rub face*	*Index*	*Nil index*
Patient	1		3	1	2
rub	2	(1+20 days)	1	1	—
face	3	(1+25 ,,)	12	6	6
	4	(1+27 ,,)	40	9	31
	5	(1+46 ,,)	32	31	1
			—	—	—
			88	48	40

This did not include rubs in the ten minutes following a fit.
Index appearing before starting to rub 7
Index appearing after rubbing stopped 24

appears 12 times out of 17 trials in the hypnotic situation when the face is not rubbed. The data presented in the 2×2 (Table IV) and the Chi square test show no significant differences in the number of responses which occur on actual rubbing of the face from those which occur from hallucinated rubbing. In other words, the index produced by actual rubbing can also be produced by the psychological means used in the second situation and these two situations do not differ with regard to the frequency of

TABLE III

A.		*Trial*	*Index*	*Nil index*
Patient rub not touching face				
	Day 1	1	1	–
		2	1	–
		3	1	–
		4	1 (Fit)	–
	Day 2	1	–	1
		2	–	1
		3	1	–
		4	1	–
		5	1	–
		6	1	–
		7	1	–
		8	1	–
		9	–	1
		10	1	–
		11	–	1
		12	1	–
		13	–	1
		—	—	—
B.		17	12	5

Day 1.—Total recording time 110 minutes, net stimulus time 11 minutes

Day 2.—Total recording time 98 minutes, net stimulus time 7 minutes

The net stimulus time is the time interval between the signal to start and the signal to stop a task. The tasks (hallucinated rubbing and others) occupied therefore only a small proportion of the total recording time.

TABLE IV

	Nil index	*Index*	*Total*
Table II ..	40*a*	48*b*	88
Table III ..	5*c*	12*d*	17
	45	60	105

$\chi^2 = 0{\cdot}914$.

TABLE V

	Total	*Index*	*Nil index*
Someone else rubbing patient's face .. (Unhypnotized—2 days)	6	–	6
Patient rub left and right hands .. .. (Hypnotized no specific suggestion)	6	1	5
L. G. touch patient's face (Hypnotized)			
Without suggestion	1	–	1
With suggestion	1	1	–

occurrence of the index although the physical stimulus is a specific one whereas the psychological stimulus is less so. The psychological stimulus is therefore just as effective as the actual rubbing.

(3) The patient was instructed to rub the back of his left hand with his right: this did not consistently produce the index, Table V.

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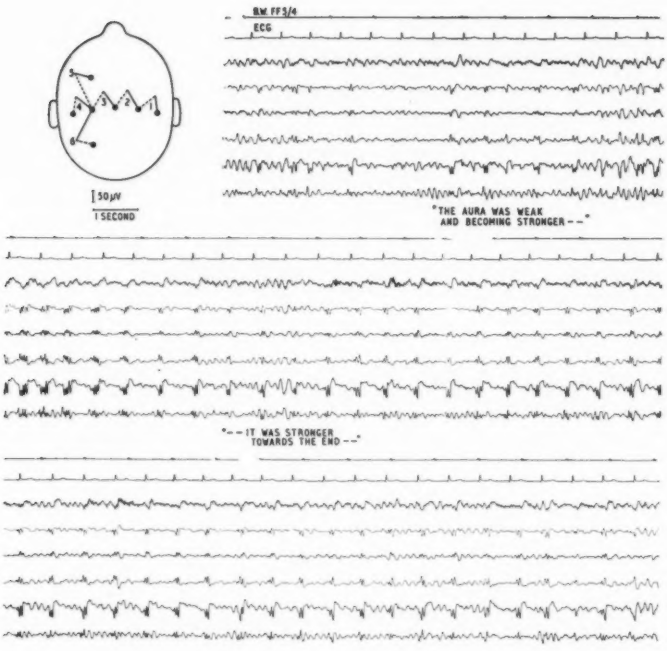

FIG. 3A.—The hypnotized patient was describing the aura experienced during the preceding task. The record is continuous. The spiking activity associated with the preceding task did not qualify within the criteria (*see* text) to be counted as an index.

(4) The index as defined, appeared unequivocally on 22 occasions during discussions with the patient totalling two-and-a-half hours (figs. 3A, and 3B). On 5 of these occasions he had been told to imagine the fit (*see below*). As already described, episodes during which the index appeared in the EEG were identified, then correlated with the tape recording and the topics of conversation noted. The duration of the index was usually of the order of five to ten seconds on each occasion, but sometimes lasted for up to forty-five seconds: the episodes of conversation varied in length and topic. A closely examined sample of two days EEG recordings and tape recordings showed the index as occurring at the following points in conversation:

Day 1.—(*a*) *Normal Waking State*

(i) In trying to show that epilepsy is not the only instance where a person is affected by unknown forces, the example being given of a person fainting at the sight of an accident, and followed by "you are taken over by something over which you have no control." The patient said "yes" as the index appeared.

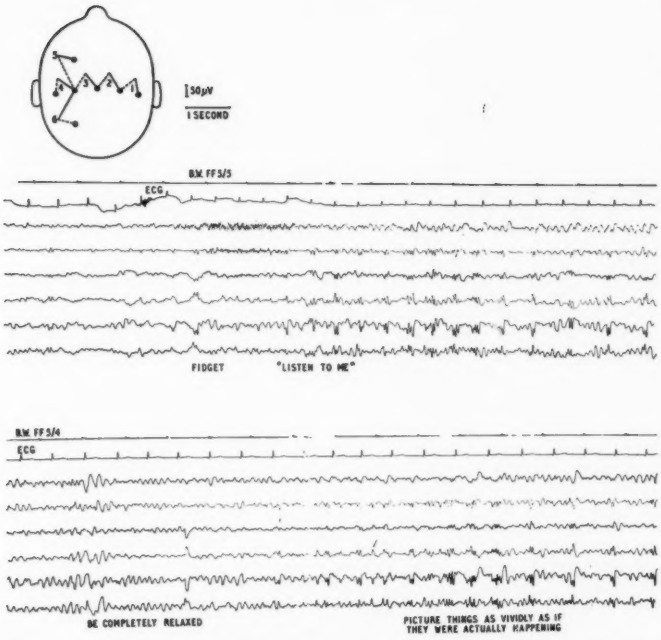

FIG. 3B.—*Upper example:* The hypnotist made the remark shown, to the hypnotized patient. The slow waves appearing before the instruction "listen to me" are an artefact caused by the patient fidgeting. *Lower example:* This shows the association of the index with the instructions of the hypnotist. The two examples are from records taken on different days.

(ii) As hypnosis was begun by the statement "I want you to relax," the index appeared.

(*b*) *Hypnotic State*

(iii) On illustrating how things can appear in consciousness from where he knows not, such as on being asked the answer to seven times seven, forty-nine immediately comes to mind.

(iv) The patient still hypnotized and immobile was asked to imagine a fit as vividly as if it were actually happening.

(v) The patient after having been urged to try and imagine his fit, described the aura that he was experiencing and said "I have still got it." The index lasted for thirty seconds on this occasion.

(vi) He was urged to imagine the whole fit vividly.

(vii) Asking him to imagine the fit taking place.

(viii) He was asked again to imagine the fit, everything that went with it and to "go over the brink" (the patient's own term referring to a point of no return in the fit process).

(ix) After describing the aura without showing any response in the EEG, he was again told to imagine rubbing his hand.

XUM

(x) Using the patient's own phrase he was asked to imagine the fit and allow himself "to go over the hill" into the fit.

(xi) The patient described how he gripped himself to stop himself from going "over the hump," resulting in a marked index for twenty-five seconds.

(xii) "Imagine a fit."

(xiii) The patient describing a strong aura—"but not strong enough to push me over the hump." Index lasted for forty seconds.

Day 2.—Hypnotized

(xiv) The patient was comparing his point of no return to "pulling the trigger of a gun" and then having no control.

(xv) The hypnotist, repeating the patient's words about "pulling the trigger" and at this the index appeared.

(xvi) The patient talking of his embarrassment on coming out of a fit.

(xvii) The patient again mentioning his embarrassment on coming out of a fit.

(xviii) The hypnotist referring to the patient's epilepsy, used the phrase "your disability."

(xix) As the patient was describing his aura as having been present but weak in the preceding task, which had been to imagine a fit (fig. 3A). (This task produced a slight change in spiking activity but did not qualify within the criteria to be counted as an index.)

(xx) The patient describing his recovery from a fit as "coming back to life."

(xxi) During deepening of hypnosis when the hypnotist said "listen to me." The index lasted for eleven seconds (fig. 3B).

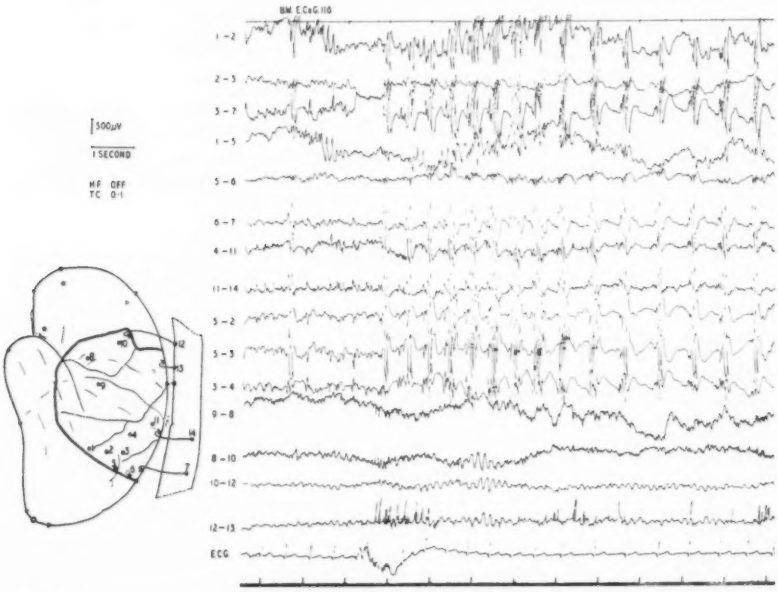

FIG. 4.—At operation a 16-channel electrocorticogram was recorded, during which the patient was asked to imagine rubbing his face (*see* text). The electrode positions are shown as numbered in the diagram and the numbers preceding the channels refer to the bipolar linkages used.

(xxii) Five seconds after awakening on a signal from hypnosis, the index was marked for forty-five seconds.

Apart from tasks the index would appear to be a response, direct or indirect, to any reference to processes affecting consciousness over which the patient had no control.

It is of interest to note that one fit occurred when the patient said "I am still afraid" à propos his fear of doctors and operations. One also occurred when he said "I still have it," referring to his fears of falling in dangerous places and being taken unawares by a fit. Seven fits were noted prior to recordings either in the ward or in the department and one on micturating during an all-day session.

(5) At operation under local anæsthesia, an electrocorticogram (ECoG) was recorded. While the record of the discharge could be expected to differ in fine characteristics from the scalp record of the index, it seems very probable that the same phenomena were being recorded (fig. 4). The patient was of necessity completely immobilized. He was asked to relax and imagine vividly rubbing his face. It was doubtful to what extent he was hypnotized. On the signal to commence there was on each of the two trials a marked change in the ECoG continuing for about fifteen seconds.

Discussion

In this study we have been concerned with an electrical response recorded in the electroencephalogram. The complexity of the EEG normally obtained is against the production of an objective measurable and repeatable response. In this case of reflex epilepsy we were fortunate in being confronted with an electrical response that was easily recognized. Ideally the electrical response used as an "index" should be (i) a recognizable response to a known stimulus, occurring within a given period following the stimulus, and (ii) different in form, character and temporal sequence from anything seen in the background record. In this case of reflex epilepsy, three types of spike phenomena were apparent (fig. 5).

(1) Spikes appearing towards the end of a clinical seizure, in the area of the lesion, lasting approximately ten seconds and occurring in a run.

(2) Focal localized spikes occurring singly and in a random manner in the area of the proven lesion. At times they were seen at about one-second intervals, on other occasions appearing at random throughout the recordings separated by intervals of up to approximately one minute in the resting record.

(3) Multiple grouped spikes, localized and focal in the area of the lesion, occurring when the patient rubbed his face. The distinctive form of the multiple grouped spikes (the index) seen when the patient rubbed his face was a clearly recognizable electrical response to the stimulus (figs. 1 and 5). Evoked fits were preceded by the index and ended with a run of spikes (1 above) both in the same area. The index was therefore related to the ictal activity and not to a diurnal or longer cycle of excitability during the three months study.

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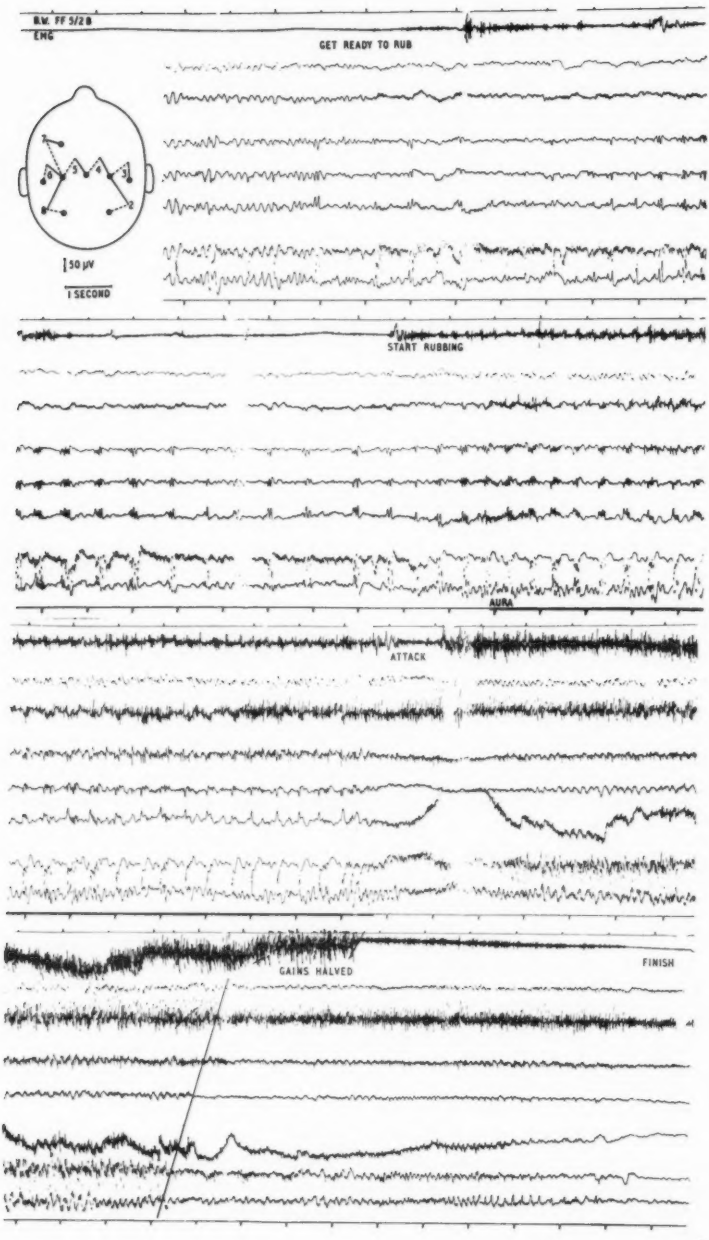
R.M. FF 5/2 B
EMG
GET READY TO RUB
50 μv
1 SECOND
START RUBBING
AURA
ATTACK
GAINS HALVED
FINISH

FIG. 5.

The results show that the index appears when the patient himself rubs his face: it also occurs when he anticipates doing this. Furthermore, without touching his face, but hallucinating this action when hypnotized, the index is clearly reproduced. Finally, when completely immobile under hypnosis and at operation, imagining the event produced marked responses. It is of interest to note that during periods of infrequent fits psychological stimuli were more effective in producing spike activity than rubbing the face. These observations would appear to confirm the view that the "reflex" act was not itself the necessary or absolute cause of the electrical response in the left parietal area.

It now seemed profitable to examine in more detail the psychological situation to which the index was a response since the physical "reflex" act was not prepotent. The index would therefore seem to be a response to the whole or some aspect of the situation as it is perceived by the patient, and the meaning of the act may be as important as the act itself. In this case it cannot be denied that the occurrence of the index is related to the pathological lesion. It is similar in some respects to the discharges set up in the neighbourhood of biochemical and structural lesions in animal experiments using strychnine, penicillin, alumina cream (Baglioni and Magnini, 1909; Amantea, 1932; Clementi, 1929, 1935; Moruzzi, 1941; Kopeloff *et al.*, 1942, 1947; Pope *et al.*, 1947; Poggio *et al.*, 1957).

In recent years there has been a considerable amount of work on the responses, in animals and man, to peripheral stimuli and it is clear that there is a mechanism which results in the apparent inhibition of peripheral and cortical responses to such stimuli. A response at the cortex to a peripheral stimulus can be modified in a variety of ways, e.g. by stimuli in another modality, or the degree of inhibition may be increased more by "significant" (Hernandez-Peon, 1957) than by unphysiological artificial and unnatural stimuli. This work is mentioned to indicate a trend towards considering more than the physical attributes of a stimulus, the way in which the stimulus is perceived by the subject. In animals and man therefore the possibility now arises of applying physiological methods to the study of what have been until now considered psychological subtleties outside the realm of physiological experimentation. More cannot be said about the relationship of this work to the phenomena we have observed

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FIG. 5.—In this example the patient was asked to rub his face and an attack resulted. The EMG was recorded from the left wrist. When the patient had the aura he pressed a button which recorded as a black line on the lower time marker. The recording is continuous and the events are as marked. This example shows that there were: (i) Random spikes in the area of the lesion during the resting record. (ii) Multiple grouped spikes appeared in the same area (the index) when the patient rubbed his face. (iii) Single spikes occurring in a run towards the end of the attack (Channel 8). It is of interest to note that spikes were suppressed as the attack commenced.

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since it is concerned with the inhibition of a cortical response whereas we have been concerned with producing rather than inhibiting a response to peripheral stimuli. One might speculate that the same mechanism is involved and that our manœuvres decrease inhibition. It has already been shown that cortical responses can be modified by verbal stimuli, Livanov, Stralchuk, Melekhava (1953), Nevsky (1954), as can subcortical responses in human beings, Hernandez-Peon and Donoso (1957), Hagbarth and Höjeberg (1957), Jouvet and Courjon (1958). In Hernandez-Peon's and Jouvet's experiments verbal suggestions in conscious patients were shown to increase or decrease the cortical response to a light stimulus of constant intensity. Problem solving and various emotional states were also shown to modify cortical responses to light flashes. These studies and the present work suggest that a description of a stimulus-response situation is incomplete without reference to the condition of the subject at a particular time. This is really to say that perception depends upon:

(1) The character of the stimulus.

(2) The functional integrity of the sensory pathways.

(3) The "particular psychological condition" of the person at the time that the perception takes place. In effect, to neurophysiology we are applying Niels Bohr's theory when he says that it is impossible to speak in an unambiguous way of the attributes of objects independent of the conditions under which they are observed, Bohr (1934, 1958). This statement would apply to both the subject and observer and in this paper we have attempted the twofold task of relating the cortical response to the psychological condition of the patient and in the first and second parts of our experiments have suggested that the response is to a stimulus as it is perceived and not wholly to the physical attributes of that stimulus. In Hernandez-Peon's experiments on animals, a stimulus is considered to be "significant" when the response to that stimulus is marked when compared with others that produce little or no response. Similarly in the interview situation certain topics may be adjudged "significant" because of the appearance of the index. Here the fit may be perceived by the patient as part of a process which renders him helpless. Thus other situations may be perceived in the same way, and similar emotions experienced, for example, when he feels controlled by doctors, operations, epilepsy and hypnosis and fears them.

Summary

(1) A patient is described who rubbed his face which produced in addition to fits, distinct spiking activity in the EEG, here referred to as the "index." Variations in this association occurred, and it was shown that the aura had no consistent relationship to the spiking activity. A clinical seizure was always followed by a refractory period for spikes.

(2) When the patient was instructed at regular intervals to rub his face,

the unexpected doubling of the interval between the instructions "get ready to rub" and "start rubbing" caused the index to appear whilst he was still immobile, on three occasions. Under hypnosis the index appeared when the patient made the rubbing movement without touching his face and it was shown that this was not dependent upon any obvious cycle of excitability or conditioning process. It was confirmed statistically that this psychological stimulus was just as effective as actual rubbing. The index was recorded during discussions with the patient and appeared to be related to certain topics or situations. The nul hypothesis that the indexes occurring in response to psychological stimuli could have occurred by chance alone was tested and shown to be highly improbable.

(3) At operation the electrocorticogram recorded the index on the two occasions that the patient was asked to imagine vividly rubbing his face.

(4) These observations are discussed and appear to support the hypothesis that the electrical response in the left parietal area to the reflex act of rubbing the right face could also be produced by psychological means alone. The electrical activity (the index) thus influenced, appeared to arise from the neighbourhood of a sub-cortical angiomatous malformation in the left parietal area.

ACKNOWLEDGMENTS

We wish to thank Dr. Denis Hill for his guidance and encouragement during the preparation of this paper. Thanks are also due to Mr. Murray A. Falconer, whose kindness and co-operation made this study possible, and to Mr. A. E. Maxwell for his statistical help.

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UPPER BRAIN-STEM COMPRESSION AND FORAMINAL IMPACTION[1] WITH INTRACRANIAL SPACE-OCCUPYING LESIONS AND BRAIN SWELLING

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PART I

UPPER BRAIN-STEM COMPRESSION

DURING the last four years the brains have been examined, after formalin fixation, from some 2,800 autopsies in two large general hospitals and one hospital for the chronic sick. As part of an investigation of the pathology of cerebrovascular disease, particular attention has been paid to the lesions which might give rise to those disturbances of mental and neurological function and to the vital signs which herald the death of a patient with an intracranial space-occupying lesion or swelling of the brain.

A large number of brains have been examined from patients who showed no evidence of neurological disease during life and no abnormality of the brain after death. This series of normal brains has been used as controls. Many of the patients with space-occupying lesions had been studied in the wards.

HISTORICAL REVIEW

Following Penfield's studies of the functions of the cerebral cortex (Penfield and Rasmussen, 1950), it has been generally accepted that lesions responsible for these signs were to be looked for in the brain-stem. In 1902 Cushing ascribed these signs to impaction of the cerebellar

[1]Collier (1904) likened the deformity of foraminal impaction to a cone shaped plug and since then the term "pressure cone" has been widely used. While it is acceptable when applied to the deformations occurring around the foramen magnum, it is an inadequate and confusing description of deformations of the upper brain-stem. Under no circumstances do they bear any resemblance to a cone-shaped plug. Upper brain-stem compression is the term used in this laboratory, and while it fails to describe the mechanism of all the associated false localizing signs, it does describe the essential morbid anatomy. Foraminal impaction was the term used by Cushing (1902) and Meyer (1920) and is more descriptive than cerebellar pressure cone.

XUM

tonsils and medulla oblongata in the foramen magnum, a deformation which became known as the cerebellar or tonsillar pressure cone. Its importance will be discussed in some detail in the second part of this paper. Meyer (1920) published a series of photographic illustrations of all the major hernias of the brain. Vincent *et al.* (1936) described the hernias of the temporal lobe through the tentorial space as the temporal pressure cone. They postulated that the mid-brain was squeezed at this level by these hernias in the same manner as the medulla at the foramen magnum by herniation of the cerebellar tonsils in the tonsillar pressure cone. Vincent, and Jefferson (1938), were more impressed by herniation of the temporal lobe anterior to the mid-brain, herniation of the uncus. Johnson and Yates (1956*a*) emphasized the importance of herniations of temporal lobe posterior to the mid-brain. Le Beau (1938) described upward herniation of the anterior lobe of the cerebellum through the posterior part of the tentorial space, compressing the mid-brain from behind. Johnson and Yates (1956*a*) recognized that downward movement of the mid-brain through the tentorial space was present in some degree in all these patients, and showed illustrations of a case without uncal hernias in which the third nerves and the pituitary stalk had been crushed against the dorsum sellæ and petroclinoid ligaments by this displacement. In the meantime a lively controversy had developed about the vascular lesions which may be found in these patients, particularly the pontine hæmorrhages secondary to massive cerebral hæmorrhage, described by Attwater (1911). Good evidence that at least most of them were arterial in origin was produced by Johnson and Yates (1956*b*) and they also reproduced them experimentally by injecting radio-opaque material into the arteries of brain-stems freshly removed at autopsy while the brain-stems were deformed. They showed clearly that deformation of the brain-stem could rupture the small arteries within its substance.

Dott and Blackwood (1951) and Blackwood (1958) showed that if the brain was fixed *in situ* by perfusion of the arteries with formalin, dissections of the region of the tentorial space revealed remarkable vascular distortion (fig. 1).

They found that the brain-stem moved down much further in relation to the tentorium than had been suspected. The basilar and posterior cerebral arteries were unable to move as far because the latter vessels were anchored to the undersurface of the temporal lobe and to the internal carotid arteries by the posterior communicating arteries. This led to stretching of the small branches of the basilar and posterior cerebral arteries. This work was important because it emphasized the downward movement and that brain-stem lesions might be produced by a mechanism other than compression by herniated temporal lobes through the tentorial space, but the vascular stretching was probably an artefact. A brain

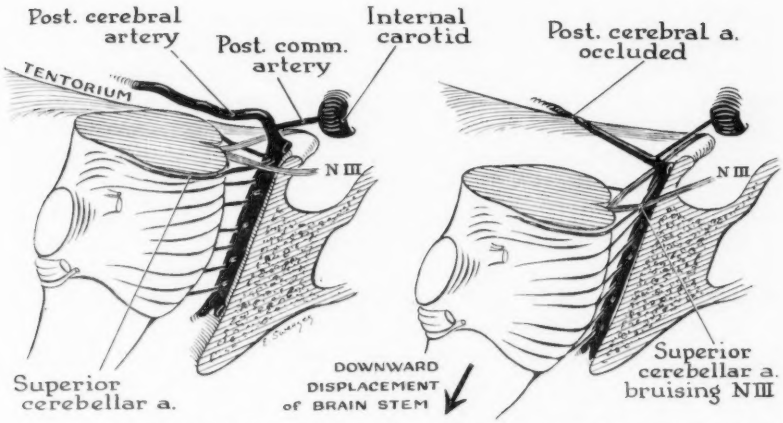

FIG. 1.—Stretching of the small branches of the basilar and posterior cerebral arteries by downward movement of the brain-stem. (Dott and Blackwood, 1951.) It is not believed that this much downward movement occurs in disease.

weighs 100 to 200 grammes more after fixation in formalin, and this increased swelling caused deformity additional to that which had already killed the patient. Angiograms in patients with space-occupying lesions have failed to confirm the presence of this vascular stretching.

ANATOMICAL VARIATIONS IN THE NORMAL

Some anterior temporal or uncal hernia was nearly always present. The sagittal groove formed by the indentation of the free edge of the tentorial space in the undersurface of the uncus might be absent, but was often 1·5 cm. long. It was usually shallow, though it might be deep, with infarction of the cortex beneath it in patients with chronic bronchitis and emphysema. However, these brains should not be considered normal, as episodes of cerebral swelling have probably occurred during periods of anoxia or carbon dioxide narcosis. The distance from the medial tip of the uncus to the sagittal groove might be 1 cm. Hernia of the temporal lobe through the tentorial space posterior to the mid-brain was found in about one brain in five. Bilateral anterior and posterior temporal lobe hernias were found on several occasions and were often asymmetrical. Hernia of the anterior lobe of the cerebellum through the posterior part of the tentorial space, with a well-marked groove on its superior surface, was not uncommon. Though some herniation through the tentorial space was normal, deformation of the shape of the brain-stem, and vascular lesions within it, or in the herniated tissue were not normal. No adequate measurement of the normal position of the mid-brain has been found in the formalin-fixed brain. Commonly the mammillary

XUM

bodies lie at a higher level than the tuber cinereum because of the tilt of the floor of the third ventricle, and if they were found at a lower level this might be evidence of downward movement. The standard coronal cut through the colliculi of the mid-brain was made by a horizontal cut through the peduncles just below the mammillary bodies. Occasionally this cut would pass through the lower part of the third ventricle, and this was always evidence of gross downward displacement. An indirect measurement of downward displacement could, however, be obtained by studying the convolutions over the convexities. If the space-occupying lesion was large enough to push the convexities so firmly against the dura that the normal smooth curve between sulcus and convolution was transformed into a sharp right angle, an equal and opposite force must have been present, pushing the brain-stem downwards through the tentorial space. Flattening of the convolutions was never found in normal brains, but occasional normal brains were found with the mammillary bodies lying below the tuber cinereum, and significant downward movement of the brain-stem might be present without the third ventricle appearing in the coronal cut through the cerebral peduncles. Another deformity was encountered which was interpreted as indirect evidence of downward displacement of the brain-stem, though it was occasionally seen in normal brains. This was a gross angulation of the brain-stem at the level of the pons, the long axes of the mid-brain and the medulla meeting at a right angle. This deformity must be to some extent an artefact because it would appear from examination of the formalin-fixed brain that the medulla protruded through the back of the patient's neck. However it was a sufficiently constant artefact to have some significance, though it was an unreliable indication of downward movement of the brain-stem, unless associated with flattening of the convolutions.

The Syndrome of Upper Brain-stem Compression

Some 150 examples of upper brain-stem compression have been examined, approximately 5 per cent of all the patients coming to autopsy. Though there were many examples with primary and metastatic tumours, intracranial hæmorrhage and swollen cerebral infarcts were the most common space-occupying lesions in this material. In many cases the patients were examined in the wards during life. A large group showed massive hernias of the temporal lobes, either anterior or posterior to the mid-brain, much deformity of the brain-stem, and hæmorrhages or infarcts in the pons, mid-brain, dentate nucleus, posterior diencephalon, or the cortical territory of one or of both posterior cerebral arteries, and often infarction of the herniated tissue itself. From these cases with unequivocal pathological findings, the syndrome of upper brain-stem compression could be defined. Though several examples of hæmorrhagic

infarction of herniated anterior lobe of cerebellum were found, no case was recognized in which the brain-stem appeared to be distorted by this hernia.

Though the syndrome was complex and variable, its main features were sufficiently constant for it to be accurately distinguished from other diseases causing coma, in the majority of cases. Increased headache, vomiting, and stiffness of the neck usually developed at the onset. The most constant feature was a global impairment of all mental functions progressing, fast or slowly, through lethargy, drowsiness and confusion to a semi-comatose state, in which the patient responded only sluggishly to painful stimulation. However, patients often died before they became as unresponsive as in surgical anæsthesia, and therefore death could not be ascribed to coma except when severe aspiration or hypostatic pneumonia developed.

Brachycardia was less frequent than tachycardia. Some fever was usual, and hyperpyrexia very common. A rise of blood pressure was not invariable and indeed the pressure might fall to become unrecordable. In most of these patients, massive gastro-intestinal hæmorrhage from acute œsophageal, gastric or duodenal ulcers was found at autopsy, in spite of very little vomiting of blood during life, but one patient was seen with severe hypotension without gastro-intestinal hæmorrhage or any apparent cause other than the upper brain-stem compression itself. Of changes in the vital signs, the respiratory disturbance was most constant. In rapidly-developing upper brain-stem compression, sudden respiratory arrest might be seen, and occasionally this followed a phase of slow, shallow, grunting respiration. This was attributed to direct damage to the respiratory mechanisms in the brain-stem. More frequently respirations increased in rate and depth, and at the same time the patient became a little cyanosed, and might cough up some frothy pink sputum, characteristic of pulmonary œdema. Later, respiration was noisy and laboured, and the accessory muscles of respiration were employed. Apnœic pauses and sighing might occur. Finally the breathing became slow and gasping before it stopped. These respiratory changes were associated with the autopsy findings of heavy congested œdematous lungs with copious bronchial secretions. The respiratory disturbances seen in life were believed to be the reaction to the pulmonary and bronchial changes and not the cause of them, because they are very similar to respiratory disturbances in other conditions with congestion and œdema of the lungs and bronchi. Death was usually caused by the respiratory disturbance, though it might rarely be secondary to hypotension.

Of the neurological signs two were of great importance. Loss of the pupillary light reflex was very constant, though occasionally it was not

XUM

found until the compression was far advanced. Rarely the reflex might be lost first on the side opposite the space-occupying lesion, though the converse was the rule. Dilatation of the pupil was usual, but many patients were seen in whom the pupils remained small or even contracted. The pupillary changes were usually a good indication of the advance of the brain-stem compression, but one patient was seen with a fixed dilated pupil, secondary to swelling of the right hemisphere, who was alert enough to carry on a sensible conversation and give an accurate account of his illness. Decerebrate rigidity was common, and it was exceptional to be unable to detect some extensor spasm in the limbs in response to painful stimulation at some stage in the course of the illness. Nystagmus was seen only once.

When the brain-stem compression developed more slowly in patients with cerebral tumours, false localizing signs might be seen which were attributed to these displacements. Mild cerebellar ataxia of the legs was the most common. Extensor plantar responses and cranial nerve palsies from three to six inclusive were common. The homo-lateral hemiplegia of Kernohan and Woltman (1929) was rare except in cases of subdural hæmatoma.

Basilar artery thrombosis did not mimic this syndrome. The infarction was mostly confined to the basis pontis or cerebral peduncles and consequently the coma in the early phase of this disease was more apparent than real. Though the patients had a complete quadriplegia and anæsthesia, they might be able to move their eyes on command and corneal reflexes were often brisk. These reflexes were nearly always absent when total paralysis of the limbs was a product of deep coma. However, 3 patients with hypertensive cerebral hæmorrhage into the tegmentum of the mid-brain and pons showed a state which could not be distinguished from upper brain-stem compression; and widely dilated pupils, unresponsive to light, were found because the third nerve nuclei were involved in the hæmorrhage. This clinical syndrome was never encountered except with upper brain-stem compression or when some disease process paralysed the functions of this region.

Pathological Observations

In addition to the first group of patients with marked distortion of the upper brain-stem by temporal lobe hernias, a second group was found, almost as large as the first, in which hernias of the temporal lobe were trivial or absent. The only constant abnormalities in the two groups were flattening of the convolutions against the dura mater, and a clinical syndrome of paralysis of the upper brain-stem. It was not possible to distinguish the clinical features of the first group with temporal lobe hernias from the second. In both there was some additional evidence of

downward movement of the brain-stem, such as displacement downwards of the mammillary bodies, and backward angulation of the axis of the medulla in relation to the axis of the mid-brain at the level of the pons. In one patient in the second group the calcified pineal gland was driven into the tectum of the mid-brain by downward movement of the pulvinar of the thalamus, but with this exception there was no distortion of the cross-section of the mid-brain. Three patients showed small hæmorrhages in the tegmentum of the mid-brain and pons, but otherwise no histological abnormality was detected in the upper brain-stem. It was concluded that in both groups of patients downward movement of the brain-stem was the cause of paralysis of the tegmentum of the mid-brain and pons, though hernias of the temporal lobes had produced additional compression and distortion of the mid-brain in the first group of patients. It was clear that downward movement of the mid-brain alone was an adequate cause of paralysis of the upper brain-stem.

Early in this investigation 3 patients were encountered, without significant temporal lobe hernias, with massive acute hæmorrhagic infarcts of the territory of both middle cerebral arteries secondary to embolic occlusion of these vessels. The unilateral massive middle cerebral infarct commonly swells enough to produce fatal upper brain-stem compression, usually with significant temporal lobe herniation, and in these 3 patients the swelling was twice as great. 6 patients with massive subarachnoid hæmorrhage confined entirely to the subarachnoid space are included in the second group of patients. These patients showed a clinical syndrome of paralysis of the tegmentum of the mid-brain and pons indistinguishable from that seen in the first group. Though the convolutions were invariably flattened against the dura, collections of blood in the sulci over the convexities prevented the junctions between the sulci and convolutions forming the sharp right angle so commonly seen in extreme convolutional flattening. These 6 patients illustrate the difficulty in deciding at autopsy whether a moderate degree of convolutional flattening indicates a degree of downward displacement of the brain-stem adequate to cause paralysis of the upper brain-stem tegmentum. It was concluded that moderate convolutional compression indicated significant downward displacement of the brain-stem, if the patient showed the syndrome of paralysis of the upper brain-stem but not if the patient did not show this syndrome. It might not be possible to come to any conclusion on examination of the brain alone. Minor degrees of convolutional compression do not cause significant downward movement, but patients treated with hypothermia may die of upper brain-stem paralysis and very little convolutional compression will be found at autopsy. In these patients marked convolutional flattening was present before the brain volume was reduced by treatment, which was instituted too late to save their lives.

XUM

The Mechanism of Brain-stem Compression in Pure Downward Displacement of the Brain-stem

The rarity of histological abnormality in the brain-stem and the failure to confirm Dott and Blackwood's type of vascular stretching in angiograms led to the conclusion that downward movement also produced paralysis of the tegmentum of the mid-brain and pons by compression.

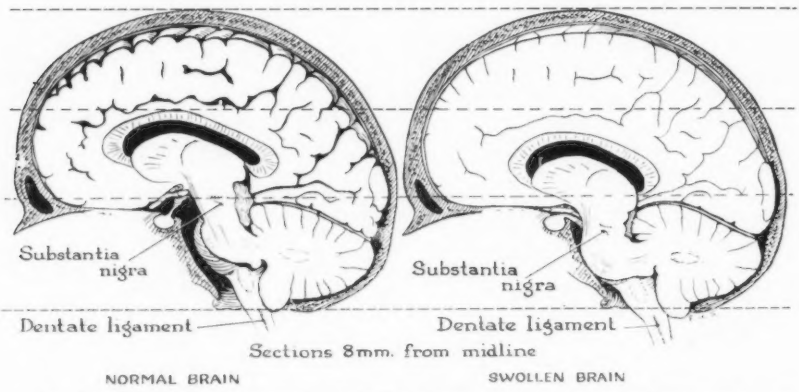

FIG. 2.—The dentate ligaments allow the upper cervical spinal cord to move down only half a centimetre. Further downward movement of the thalamus leads to buckling of the brain-stem and upper brain-stem compression. Rarely the cerebellum is so big or the foramen magnum is so small that downward movement of the brain-stem is arrested by impaction of the cerebellum within the foramen magnum. Buckling of the brain-stem may complicate the syndrome of foraminal impaction, in these patients.

The dentate ligaments allow a maximum of 1 cm. movement of the upper cervical cord from extreme upward to extreme downward displacement at autopsy. Therefore no more than $\frac{1}{2}$ cm. of downward movement can occur from the normal position. As soon as the diencephalon and mid-brain move down more than $\frac{1}{2}$ cm., the length of the brain-stem must be shortened. The white matter of the medulla, basis pontis, and cerebral peduncles resists this compression better than the grey matter of the diencephalon and the tegmentum of the mid-brain and pons. The brain-stem therefore buckles, the posterior half of the mid-brain and pons shortening more than the anterior half.

Radiological investigation of patients with space-occupying lesions has provided confirmation of downward movement of the brain-stem and the deformity it causes. Downward movement of the mammillary bodies and the third ventricle may be recognized in pneumograms. Two arched bands of air called the wings of the ambient cisterns by Liliequist (1956), may be recognized in the lateral films of pneumograms. These arched

bands consist of air bounded laterally by the choroidal fissure of the body, trigone and temporal horn of the lateral ventricles surrounding the superior, posterior and some of the undersurface of the thalamus. The posterior part of the hippocampal gyrus of the temporal lobe lies just below the choroidal fissure inferior to the pulvinar. Liliequist found that these arched bands outlining the superior surface of the thalamus and pulvinar crossed the superior colliculus or the middle of the quadrigeminal plate but never the inferior colliculus in normal patients, and this has been confirmed in a small group of dissections in normal brains. Azambuja, Lindgren and Sjögren (1956), described downward movement of the wings of the ambient cisterns in patients with cerebral tumours so that they crossed the inferior colliculus. This indicates both downward movement of the pulvinar and shortening of the long axis of the tegmentum and tectum of the mid-brain. They interpreted this abnormality as indicating a posterior temporal hernia. Though the posterior hippocampus must be displaced by the pulvinar, it is not essential to assume that it herniates medially through the tentorial space, and it often slides laterally over the tentorium.

Jefferson and Sheldon (1956) reported that the basilar artery fills from carotid arteriograms more frequently in the presence of space-occupying lesions, and this suggests that the angulated pons may compress the basilar artery against the basi-sphenoid bone enough to alter the vascular pressure relationships, though there is no evidence that this compression is enough to occlude the basilar artery completely.

In the formalin-fixed brain sagittal sections made 8 mm. from the mid-line show a deformity similar to that shown in fig. 2 in patients with flattened convolutions. The longitudinal axis of the tegmentum of the mid-brain and pons was shortened in patients with brain swelling or tumours when compared with normal brains, and this shortening accounts for the angulation of the brain-stem. In one patient in twenty-five the cerebellum is so large or the foramen magnum so small, that downward movement of the brain-stem is arrested by foraminal impaction and not the dentate ligaments.

From these observations it is concluded that the downward compression of the posterior diencephalon and tegmental grey matter of the mid-brain and pons against the unyielding medulla and upper cervical cord was the constant lesion present in both groups of patients with flattened convolutions and signs and symptoms of paralysis of the tegmentum of the upper brain-stem, whether a temporal lobe hernia was present or not.

Reid and Cone (1939) showed how the uncus might compress the third nerve in cases of uncal herniation in extradural hæmorrhage. Another mechanism paralysing the third nerves must be present in the patients without uncal herniation and Johnson and Yates (1956*b*) suggested that they might be stretched over the petroclinoid ligaments. While this

XUM

explanation seems probably correct, the third nerve nucleus may also be damaged. They also reported infarction of the pituitary produced by stretching the pituitary stalk over the dorsum sellæ and a similar case has been encountered in a patient with massive cerebral hæmorrhage in this material. If infarction may occur, a lesser degree of displacement may produce œdema of the pituitary, and this swelling may lead to erosion of the sella turcica. None of our patients with foraminal impaction showed this radiological sign of high intracranial pressure.

The Importance of Temporal Lobe Hernias

Anterior and posterior temporal lobe hernias increased the distortion of the brain-stem, at the mid-brain level, and therefore vascular lesions in the brain-stem were much more common than in uncomplicated downward displacement. Of course they added significantly to the compression, and produced a clinical effect with less downward movement. These hernias packed the subarachnoid space around the mid-brain, obstructing the flow of cerebrospinal fluid. Though no convincing examples of upward hernia of the anterior lobe of the cerebellum compressing the mid-brain were encountered there is evidence that this hernia may produce fatal upper brain-stem compression. Jefferson and Johnson (1950) report three examples of sudden coma and arrest of respiration after tapping the lateral ventricle in patients with space-occupying lesions within the cerebellum. The cingulate hernia, inasmuch as it was a product of lateral shift of the hemispheres, also increased the deformation of the mid-brain, though it was never encountered by itself.

It has not been found possible to forecast whether temporal lobe hernias would be found at autopsy when patients with upper brain-stem compression were examined in the wards. Absence of dilatation of the pupils and absence of paralysis of upward gaze were suggestive evidence that no temporal hernia would be found. No patients were encountered in this series, who showed bilateral ptosis and paralysis of upward gaze while they were fully alert. Johnson (1956*a*) reported 3 such patients, who showed marked bilateral posterior temporal hernias, and he regarded this sign as diagnostic of this deformity. Diffuse brain swelling and parasagittal tumours rarely produced a significant hernia, but exceptions have been encountered. It was not possible to confirm Johnson's (1957) observation that tumours in various places all produced characteristic deformities of the mid-brain. Many patients with embolic occlusion of the middle cerebral artery with total infarction of its territory were found in this material, who died of upper brain-stem compression. The site and volume of the infarcted swollen brain was approximately constant in these patients. Some showed no significant temporal lobe hernia at all. Others had a marked uncal hernia with displacement of the mid-brain backwards on this side relative to the opposite side. Unilateral and

bilateral posterior temporal hernias with a pear-shaped deformity of the mid-brain were seen. The last case encountered showed large anterior and posterior hernias with compression of the opposite peduncle against the free edge of the tentorium cerebelli and infarction at the site of this compression. The anatomical variations in the shape of the brain seemed to be more important in determining the pattern of herniation and mid-brain distortion than the position of the space-occupying lesion.

Vascular Lesions and the Phenomenon of Irreversible Brain-stem Compressions

One patient who died of massive cerebellar hæmorrhage, showed a clinical syndrome very similar to that of upper brain-stem compression with two exceptions. He had nystagmus, and his small equal pupils did not become fixed to light until he was so deeply comatose that all reflex responses were lost. At autopsy there was no significant temporal lobe hernia, no foraminal impaction, and only minimal convolutional compression. The anterior lobe of the cerebellum had herniated through the tentorial space, and the herniated portion was infarcted. However, when the brain-stem was cut sagittally the mid-brain showed no compression by the upward tentorial hernia, but the tegmentum of the pons was grossly flattened and distorted by the swollen cerebellum. It contained three hæmorrhages. This case of pontine compression without other significant hernias supports the opinion of Johnson and Yates (1956*b*) that brain-stem hæmorrhages may be caused by distortion and compression (fig. 3), Plate XLII.

Hæmorrhages and infarctions in the brain-stem probably occur only when the compression is far advanced, and are more an indication of the site and degree of compression and distortion than the cause of any signs. However, they have been blamed for the phenomenon of irreversibility by Dott and Blackwood (1951). Early in the progress of upper brain-stem compression, removal of the space-occupying lesion or tapping the ventricles may produce recovery. Later the condition cannot be reversed by these procedures and the patient will die in spite of relief from the compression. In some such patients, swelling of the infarcted herniated temporal lobe may continue to compress the brain-stem. In others the tegmentum of the pons and mid-brain may be destroyed by extensive hæmorrhages and infarction. However, in most patients the vascular lesions are quite small and not incompatible with recovery. Paraplegic patients may recover in a few minutes, after excision of an extramedullary tumour. Sometimes the cord is necrotic and no recovery occurs. Most often a complete recovery follows after a delay of several days. Similarly the paralysis of function of the brain-stem tegmentum may not recover for hours or days after the compression is relieved. In fact it may persist long enough to kill the patient. Some cases of so-called

XUM

irreversible compression have shown a remarkable recovery after a delay of a day or two when treated with prolonged hypothermia (Howell, Stratford and Posnikoff, 1956).

Part II

FORAMINAL IMPACTION

In his original description of impaction of the cerebellum and medulla oblongata within the foramen magnum, Cushing (1902) suggested that the medullary compression might be responsible for those signs and symptoms which are now known to be caused by upper brain-stem compression. Except for the important papers of Meyer (1920) and Jefferson and Johnson (1950) detailed analysis of the clinical syndrome has been neglected in the literature since. However, foraminal impaction or the tonsillar pressure cone has remained familiar to neurological surgeons and pathologists. Posterior fossa decompression with excision of the arch of the atlas and opening of the dura mater is widely practised to relieve or prevent this impaction, and occasionally dramatic recovery after arrest of respiration has been achieved by this means (Johnson, 1958).

The Diagnosis of Foraminal Impaction in the Formalin-fixed Brain

The variations in shape of the undersurface of the cerebellum is so great in normal brains that during the first year of this study it was doubted whether a diagnosis of foraminal impaction could be made. Five out of six normal brains show a groove on the undersurface of the cerebellum made by indentation of the posterior rim of the foramen magnum. A pair of tongue-shaped projections of cerebellar tissue, incorrectly named the tonsils, may hang down below this rim into the subarachnoid space of the upper cervical cord, and may be more than 2 cm. long in the normal brain. They may also meet in the mid-line. However, in the group of cases to be described below, the groove formed by the rim of the foramen magnum in the undersurface of the cerebellum was exceptionally deep, and reached forward on either side of the medulla to within a few millimetres of the flocculus. Medial to the groove a narrow wedge of cerebellum was packed tightly against the olives. Only after 3 patients were seen with infarction of the herniated cerebellar tonsils, and one with infarction of the medulla itself, was it recognized that this deformity might be caused by foraminal impaction. Compression of the upper brain-stem and spinal cord may cause complete paralysis of function without any histological lesion, though hæmorrhages and infarction may occur. Therefore examples of foraminal impaction might be expected without vascular lesions. 3 patients with deep foraminal grooves and extensive herniation of the tonsils, but without infarction, were encountered in whom the clinical and pathological features could best be explained by foraminal impaction. Their case histories will be presented

after the 3 patients with foraminal impaction and infarction. Several patients who also showed this deformity had clinical and pathological features best explained in terms of upper brain-stem compression. This group included 1 patient with pure subarachnoid hæmorrhage. Another small group of patients with this deformity had no other clinical or pathological evidence of neurological disease, and there is no doubt that the deformity of foraminal impaction may be exactly mimicked by an uncommon congenital variation in the shape of the brain. This deformity is not the Chiari type I deformity (Greenfield, 1958) because the medulla is not elongated. It may be a benign form of what Spillane, Pallis and Jones (1957) have termed cerebellar ectopia.

Case Histories of the Patients with Foraminal Impaction and Infarction

Case 1.—G. W. A white male aged 34.

Summary.—Hæmangioblastoma of the cerebellum, hydrocephalic headache, minimal papillœdema, normal skull X-rays, spikes in the electroencephalogram and sudden death from medullary compression. Hydrocephalus and tonsillar infarction at autopsy.

This patient was admitted to the Queen Mary Veteran's Hospital in Montreal in September 1956, with a five month history of headache, paroxysmal vertigo in certain positions of the head, vomiting and later diplopia. In hospital he suffered from brief paroxysms of agonizing frontal headache every ten minutes, often precipitated by movement. He was alert and hungry, but afraid to eat for fear that vomiting might precipitate a headache. His speech was slurred; there was a first degree nystagmus to the right, and a little cerebellar ataxia of the right arm. The right pupil was larger than the left, but both reacted briskly to light. Papillœdema was minimal and there was no neck rigidity. The electroencephalogram showed bursts of moderate voltage sharp waves in both temporal and frontal regions associated with occasional spikes. The background rhythms were diffusely irregular. There was no erosion of the sella turcica in the skull X-rays. At 8.15 p.m. he was alert, though in severe pain. At 8.30 p.m. he was found dead.

At autopsy the right cerebellar hemisphere contained a cyst about 8 cm. in diameter containing a small mural nodule which proved to be a hæmangioblastoma. The cyst did not compress the brain-stem directly. In addition to the characteristic groove of foraminal impaction, the undersurface of the cerebellum showed bilateral tonsillar herniation of 2 cm. with hæmorrhagic infarction of the right tonsil. There was no significant herniation through the tentorial space other than a deep sagittal groove in the uncus on both sides. Though the patient showed no clinical evidence of upper brain-stem compression the convolutions were flat, the mammillary bodies low and the ventricles dilated. Except for healed pulmonary tuberculosis, no other lesions were found at autopsy.

Case 2.—M. C., male, aged 13.

Summary.—Meningoccal meningitis. Gross neck stiffness and intracranial hypertension. Hydrocephalic attack with transitory coma and residual respiratory failure, quadriplegia, dysphagia and nystagmus. Terminal gastrointestinal hæmorrhage. Infarction of the tonsils. Subependymal venous hæmorrhages.

This patient was admitted to the Montreal General Hospital under the care of Dr. Donald MacIntosh at 3.15 a.m., July 8, 1957, having developed headache and vomiting

suddenly eight hours before. He was restless, moaning and delirious, responding briskly to pain, but not to spoken commands. His neck was arched backwards. The pupils were small, equal and reacted briskly to light. The legs were flexed and the plantar responses were extensor. The temperature was 107·4° F. rectally, pulse 160 per minute, respirations 30 per minute and B.P. 100/60. The cerebrospinal fluid pressure was 400 mm. of water and was cloudy with polymorphonuclear leucocytes, a few of which were later seen to contain gramme-negative diplococci. He was treated with penicillin, chloromycetin, sulphadiazine and later hydrocortisone. Another lumbar puncture was made at 11 a.m. next morning. He slowly improved until 4.30 p.m. when quite suddenly his respirations slowed from 20 to 12 per minute and became extremely shallow. He was cyanosed. The pulse rose from 90 to 180 per minute but the blood pressure remained fairly constant at 90/40. He was totally unresponsive to any stimulus though the pupils were still small, equal and responsive to light. Artificial respiration was administered and then he was placed in a respirator continuously for the next twenty-four hours and intermittently for the remaining week of his life. One hour after this catastrophe it was noted that he had a complete quadriplegia. He slowly regained consciousness and by next morning he could open his mouth and eyes on command, but not speak. Dysphagia and a second degree nystagmus to the right were noted. Pain-sensation was found intact in the paralysed limbs on the third day of the illness. A little movement returned in the paralysed limbs by the seventh day, when he suffered a massive gastrointestinal hæmorrhage and died.

At autopsy the brain was swollen, weighing 1,650 grammes before fixation, and the convolutions were flattened. There was a well-marked bilateral and anterior and posterior temporal herniation through the tentorial space, and the mammillary bodies were low. There was no deformity of the cross-section of the mid-brain. In addition to the characteristic groove of foraminal impaction the tonsils were herniated 2 cm. and infarcted. The ventricles were small. The floor of the fourth ventricle had a granular appearance, and the elevations proved to be due to small subependymal venous hæmorrhages on histological examination. No gross or microscopic lesions were found in the brain-stem or cervical cord. The meninges showed only a trivial excess of inflammatory cells, the resolution of the meningitis being nearly complete, and therefore the brain swelling was most easily attributed to anoxia from the impaired respiration. The brain swelling was inadequate to cause the syndrome of upper brain-stem compression, though it was quite marked at autopsy.

In addition to the findings in the brain there were two acute duodenal ulcers with massive gastrointestinal hæmorrhage, perhaps attributable to the treatment with hydrocortisone. Early centrilobular necrosis of the liver and a curious patchy pneumonitis with intra-alveolar exudate of large mononuclear cells, rare polymorphonuclear leucocytes, light protein precipitate, occasional intra-alveolar hæmorrhages and fibrinoid plugs, were found.

Case 3.—*V. B., merchant seaman aged* 26.

Summary.—Probable hæmangioblastoma of the cerebellum, without papillœdema. Posterior fossa exploration with aspiration of cyst. Transitory severe hypotension. Respiratory arrest and excision of post-operative clot with recovery of respiration. Complete paraplegia, nystagmus and absent corneal reflexes. Hydrocephalic attack. Death from pneumonia. Infarction of tonsils and medulla.

This patient was admitted to the Queen Mary Veteran's Hospital in Montreal in December 1957, with a history of progressive clumsiness of the right hand, severe frontal headache, vomiting and vertigo on sitting or standing. The only abnormal physical signs were a severe cerebellar ataxia in the right limbs and a left extensor plantar response. Next day the posterior fossa was explored by Dr. H. Elliott. A marked

tonsillar herniation was seen and the posterior arch of the atlas was excised. A cyst in the right cerebellar hemisphere was aspirated but in spite of a prolonged search no mural nodule could be found. The operation was complicated by much hæmorrhage.

Two hours after operation the blood pressure quite suddenly became unrecordable, but soon returned to normal levels.

Three and a half hours after operation his breathing stopped and the wound was reopened under artificial respiration. After an extradural hæmatoma and a large hæmatoma within the cyst cavity had been evacuated, spontaneous, irregular, shallow respirations returned at a rate of twelve per minute, both costal and diaphragmatic components being present. Two hours after the wound was reopened, he half opened his eyes. There was a slow nystagmus at the rate of twenty beats per minute. The eyes moved slowly downwards from approximately 45 degrees above to 60 degrees below the horizontal, and the quick returning phase of the movement was associated with elevation of the upper eyelids. Corneal reflexes were absent and no movement of the limbs was seen, spontaneously or in response to any form of stimulation. The pupils were equal and reacted briskly to light. Twelve hours after the operation he looked to right and left upon command. The curious nystagmus was present only when he was alert, and while asleep the eyes were deviated downwards, the right eye more so than the left. Jaw and facial movements were present, but the complete quadriplegia, speechlessness and absent corneal reflexes remained. Thirty-six hours after the reopening of the wound, he had an attack lasting not more than one or two minutes during which he was totally unresponsive, and respirations stopped. He became cyanosed and the eyes deviated fully downwards. The pupils were widely dilated and fixed to light. B.P. 165/85, pulse 116 per minute. After this hydrocephalic attack the eyes returned to the forward position and the pupils became small and equal, and responded briskly to light. Two days after the first reopening of the wound it was reopened again, and more blood-clot was evacuated. He remained unresponsive after this operation in spite of treatment with prolonged hypothermia at a rectal temperature of between 30° C. and 32° C. Intermittent artificial respiration was required. He showed a little return of voluntary movement in all four limbs on the eighth day after the original craniotomy, and died on the tenth day.

At autopsy the ventricles were not dilated and there was no flattening of the convolutions or herniation of the temporal lobes through the tentorial space (fig. 4). A large mass of blood-clot replaced much of the right cerebellar hemisphere. There was hæmorrhagic infarction of a portion of the anterior lobe of the cerebellum which had herniated upwards through the tentorial space, but there was no evidence that this hernia or the cerebellar hæmatoma had compressed or distorted the brain-stem. The cerebellar tonsils were herniated about 1½ cm. and were both infarcted. The characteristic groove of foraminal impaction was present though the posterior rim of the foramen magnum and the posterior arch of the atlas had been excised. The dura had been closed after the first craniotomy and it is presumed that the posterior part of this groove must have been made by indentation of the dura. Sagittal sections of the brain-stem showed a pale softening approximately 1 cm. long, 6 mm. deep and 5 mm. wide in the rostral posterior portion of the closed medulla. It was assumed that the patient had a small hæmangioblastoma nodule, but it could not be found. In addition to the findings in the brain, the posterior two-thirds of both lungs were consolidated with bronchopneumonia.

Case Histories of Patients with Foraminal Impaction, but without Infarction

Case 4.—*P. F., a Ukrainian male, aged* 60.

Summary.—Acoustic neuroma presenting with pyloric stenosis. Hydrocephalic headache. Electroencephalogram showing sharp waves and persistent slow-wave focus. Dysphagia developing late and papillœdema only terminally. Hydro-

XUM

cephalic attacks precipitating upper brain-stem compression and unexpected death.

This patient was admitted to the Montreal General Hospital in May 1955, with a history of six months progressive epigastric pain and vomiting. For one month he had suffered from occasional severe suboccipital and frontal headaches lasting only a few minutes. On admission the only abnormal signs were mild conduction deafness in the right ear and moderate cerebellar ataxia in the right limbs. He developed a mild dysphagia. Skull X-rays were normal. Two electroencephalograms showed a poorly regulated alpha rhythm with intermittent fast activity, sharp waves and occasional diffuse bursts of 5 to 6 per second activity. There was a constant moderately high-voltage slow-wave focus in the left temporal region. A series of four radiological investigations of the stomach after a barium meal showed an indefinite filling defect in the pylorus, and progressive pyloric obstruction. It was decided to explore the abdomen first, but no carcinoma was found at laparotomy. Next day there was minimal papillœdema for the first time, and he was drowsy and confused. The right plantar response was extensor, the neck a little stiff, and he showed bilateral ptosis and loss of upward movement of the eyes. Extensor spasms of the arms were noted in response to pinching the finger nails. One hour later these signs were not to be found, and he was fully alert and sensible. Six hours later he was found totally unresponsive without tendon jerks, plantar responses or corneal reflexes. The pupils were widely dilated and fixed to light. He was cyanosed with respirations 36 per minute, pulse 120 per minute, B.P. 122/78. He died shortly afterwards.

Except for congestion and œdema of the lungs the only significant findings at autopsy were in the brain. A large multiloculated cystic neurofibroma approximately 5 cm. in diameter was attached to the right vestibular nerve. It had burrowed deeply into the substance of the right cerebellar hemisphere, causing only a shallow indentation of the lower pons and upper medulla on the right side. In addition to the characteristic groove of the foraminal impaction there was a marked dilatation of the entire ventricular system, and gross flattening of the convolutions. Except for deep sagittal grooves in the uncus, there was no evidence of significant herniation into the tentorial space. The mammillary bodies were low, confirming the clinical impression that death was actually caused by upper brain-stem compression, secondary to hydrocephalus.

Case 5.—W. F., housewife aged 67.

Summary.—Metastatic carcinoma of the cerebellum. Bilateral deafness and hydrocephalic attack with coma followed by complete deafness. Death from carcinomatosis.

This patient remained well after a resection of an adenocarcinoma of the colon in 1949 until she was found to have a local recurrence with pulmonary metastases in January 1957. A cold in February 1957 was followed by severe paroxysmal coughing and increasing bilateral deafness. One evening she fell unconscious during a paroxysm of coughing and was unrousable. She recovered consciousness in two hours but the deafness was extremely severe. In three days the cough recovered and the hearing returned to normal. She died, emaciated and jaundiced, in September 1957 without further neurological symptoms.

At autopsy, in addition to multiple metastases in the liver, lungs, thyroid and adrenal glands, a cystic metastatic tumour $5 \times 3 \times 2$ cm. in size was found in the anterior lobe and vermis of the cerebellum. The characteristic groove of foraminal impaction with herniation of the tonsils, 2 cm. below the rim of the foramen magnum was found, but the convolutions were not flattened and there was no other hernia of the brain. It was concluded this deformity gave rise to symptoms only during an episode of brain swelling caused by respiratory infection.

XUM

Case 6.—J. L., French Canadian male aged 18.

Summary.—Tuberculous meningitis with two spontaneous partial remissions and a polymorphonuclear leucocytosis. Progressive intracranial hypertension, neck stiffness and bilateral palsies of the seventh, eighth and tenth cranial nerves during the second remission. Hydrocephalic headache and transitory amaurosis. Sudden unexpected death.

This patient was admitted to the Montreal General Hospital, December 27, 1957, with a two-week history of headache, nausea, vomiting, fever, lethargy and neck stiffness. He had received some pills, and had improved until the day before admission, when his eyesight deteriorated so much that he was unable to read. On the day of admission he quite suddenly became delirious, confused, restless and hallucinated. The temperature was 101° F. rectally, pulse 100 per minute, respirations 24 per minute and blood pressure 114/70. The neck was stiff and he frequently held his head as if in agony. No other abnormal signs were detected. Lumbar puncture under sedation showed a cerebrospinal fluid pressure of 480 mm. of water. The c.s.f. contained 700 white cells per c.mm. (20 per cent polymorphs and 80 per cent lymphocytes). Protein 232 mg. per 100 ml., chlorides 99 m.eqv. per 100 ml. and glucose 24 mg. per 100 ml. Because of a marked polymorphonuclear leucocytosis in the blood (W.B.C. 19,000 cells per c.mm.) and the improvement with the treatment outside hospital, it was decided that he might have a pyogenic meningitis modified by inadequate treatment rather than tuberculous meningitis. This error received apparent confirmation when he appeared to respond to vigorous treatment with chloromycetin, penicillin and sulphadiazine. The temperature returned to normal and he became alert, sensible and could co-operate fully in examination. The cell count in the cerebrospinal fluid dropped to 125 c.mm., 90 per cent lymphocytes. However the neck stiffness increased and the cerebrospinal fluid pressure rose to 550 mm. of water while he lay relaxed on his side. On the fourth hospital day he developed a bilateral facial palsy, a second degree nystagmus to the right and a little bilateral deafness which became more severe. On the fifth day he had difficulty in swallowing and vomited once. It was then noted that he was unable to remember events one hour before, in spite of being alert and sensible, a mental state regarded as so characteristic of tuberculous meningitis that it was decided to begin specific treatment. At 6 p.m. that evening he coughed while a gastric tube was passed and held his head because of agonizing pain. At 7.30 p.m. he was alert and sensible and no urgency was recognized. Ten minutes later he was found dead.

At autopsy the brain was large, weighing 1,540 grammes before fixation. The convolutions were only moderately flattened, and there was no significant herniation through the tentorial space. The cerebellar tonsils stretched $1\frac{3}{4}$ cm. below the groove in the undersurface of the cerebellum formed by the rim of the foramen magnum, but there was no infarction. This groove had the characteristics of foraminal impaction (fig. 5). The flocculus was unduly large and prominent on both sides, and appeared to compress the seventh and eighth cranial nerves emerging rostrally, and the ninth nerve and lateral recess of the fourth ventricle emerging caudal to it. There was much exudate in the chiasmatic and interpeduncular cisterns, but very little in the cisterns below the tentorium. The ventricular system showed only a little dilatation and there was some granular ependymitis of the floor of the fourth ventricle. Under the microscope the exudate showed the characteristic features of tuberculous tissue and a tubercle bacillus was later recovered by guinea-pig inoculation of the original specimen of cerebrospinal fluid. The lungs showed the same curious patchy pneumonia found in Case 2, but otherwise there were no significant findings in the rest of the body.

XUM

Clinico-pathological Correlation

4 of these 6 patients showed pathological evidence of upper brain-stem compression in addition to foraminal impaction, and in the fourth it was of undoubted clinical significance. Before the syndrome of foraminal impaction could be disentangled it was essential for the clinical syndrome of upper brain-stem compression to be clarified, and an attempt has been made to do this in the first part of the paper. Fortunately only the fourth patient showed any evidence of direct brain-stem compression by the tumour, and in his case it was slight. Some of the cerebellar ataxia and the severe vomiting with a "functional" pyloric stenosis may be attributed to this, and the deafness was also caused by the tumour by mechanisms other than foraminal impaction or upper brain-stem compression.

The syndrome of foraminal impaction may be divided into those signs and symptoms attributable to vascular distortion caused by the impaction, cranial nerve palsies, medullary compression and the peculiar fluctuating hydrocephalus.

(1) *Vascular Distortion*

Suboccipital pain was only specifically recorded in the fourth patient, though some others were never in a state to give an accurate description of their symptoms. Neck stiffness on flexion was noted in three patients, but it was absent in the first and third patients. Pain referred to the suboccipital region or high cervical spine from intracranial disease must indicate involvement of the pain sensitive large vessels or nerves carrying pain fibres. Distortion of the posterior inferior cerebellar artery has been recorded in angiograms in these patients (Löfgren, 1956) and is presumably the source of the pain. Neck rigidity from spasm of the posterior neck muscles is analogous to abdominal rigidity in painful conditions within the abdomen and is presumably a nociceptive reflex. Nerve roots withstand contact with purulent exudate extremely well, but any inflammation within the subarachnoid space must also involve the adventitia of arteries and veins within it, and it is presumed that this is the major cause of pain and neck rigidity in meningitis. The increasing neck rigidity in the sixth patient in spite of remission in the meningitis, was evidence of increasing vascular distortion of the vessels of the posterior fossa. It is improbable that the herniated tonsils displaced high cervical nerves. The vertebral artery must be compressed to some extent as it passes through the foramen magnum in foraminal impaction, and this may account for the intracranial bruit recorded by Meyer (1920). No such bruit was heard in our patients. Thus clinical evidence of vascular distortion or compression may be found in this condition, but it may be absent.

(2) *Cranial Nerve Palsies*

Transitory bilateral eighth nerve palsy with deafness is the most

common palsy recognized by the patient. The dysphagia in the second, fourth and sixth patients was probably due to bilateral partial tenth nerve palsy. The bilateral seventh nerve palsy in the sixth patient was eventually complete. In foraminal impaction the seventh and eighth nerves emerging rostal to the flocculus and the ninth nerve caudal to the flocculus, are particularly liable to compression against the adjacent cerebellar tissue by the flocculus, if it is large. Ninth nerve palsies have probably been overlooked. No eleventh or twelfth palsies have been seen, either in these patients or clinically diagnosed examples of foraminal impaction. The cause of the diplopia in the first patient is unknown, but minimal sixth nerve palsy secondary to downward movement of the brain-stem is the most likely explanation. The cranial nerve palsies have all been bilateral in these patients. They may be absent.

(3) *Medullary Compression*

A progressive global impairment of consciousness which is the dominant feature of upper brain-stem compression, is no part of this syndrome. The patient may be alert one minute and dead the next, as in the first and sixth cases. When coma is seen it may last only a minute or two, as in the third patient, or several hours as in the second, fourth and fifth patients. In the fourth it was almost certainly secondary to upper brain-stem compression, and this possibility is difficult to exclude in the others. However, there is evidence that lesions of the medulla may produce transitory coma. Brain (1951) reported transitory coma in a patient with thrombosis of the posterior inferior cerebellar artery and Cairns (1952) described repeated transitory attacks of coma in a patient with a glioma of the high cervical cord spreading into the lower medulla. He also quotes a patient of Reichardt's, who suffered a brief attack of coma with brachycardia after a cisternal puncture needle had pierced the medulla.

The respiratory disturbance in these patients is quite distinct from that most commonly seen in upper brain-stem compression. The respiration becomes slow and shallow, or may suddenly be arrested. The innervation of the respiratory muscles is disconnected from the respiratory mechanism of the brain-stem and the sudden slowing of respiration must indicate direct damage to the respiratory centres. As Jefferson and Johnson (1950) have commented, the disturbance of respiration in upper brain-stem compression is so noisy that it can never be overlooked by the nursing staff, while respiratory disturbance in these patients is silent. In some, it is the probable cause of death, but in one patient, not included in this series, death was witnessed, and no pulse or heart beat could be detected within thirty seconds of the respiratory arrest. Neither the first nor sixth patient was noted to be cyanosed at autopsy. It is suspected that the vasoconstrictor innervation of the blood vessels may be disconnected from the vasoconstrictor mechanisms of the brain-stem at the same time as

XUM

respiration is arrested, and the acute hypotension which results, may also contribute to the sudden death. The transitory hypotension seen in the third patient may be an example of this, but other mechanisms more commonly account for hypotension after surgical operations. Brachycardia was noted in Reichardt's patient after puncture of the medulla (Cairns, 1952) and it is possible that medullary compression may arrest the heart.

Quadriplegia was found in the second and third patient after an episode of respiratory arrest and coma, from which they had been resuscitated. The limbs were flaccid and all reflexes were absent, but some recovery was noted, with a return of tendon-jerks and extensor plantar responses, before they died. Pain sensation could be tested in the third day of the illness in Case 2. The patient learned to signal "yes" and "no" with eye movements and he claimed to feel pin-prick in the paralysed limbs. Several patients showed lateral nystagmus and the third showed a peculiar downward nystagmus and at times a downward fixation of gaze. While these disturbances of ocular movements can probably be attributed to medullary compression, the fixed dilated pupils during the hydrocephalic attack, thirty-six hours after the first reopening of the wound may have been secondary to downward movement of the brain-stem and upper brain-stem compression, or simply a product of the depth of coma. Fixed dilated pupils have been observed during major epileptic seizures. The loss of corneal reflexes in this patient must be attributed to paralysis of the descending tract and nucleus of the trigeminal nerve. The signs of medullary compression were always of a catastrophic nature. No minor involvement of long tracts was recognized.

(4) *Hydrocephalus*

Marked dilatation of the ventricular system including the fourth ventricle was found at autopsy in the first and fourth patient and mild dilatation in the sixth. However there was clinical evidence of hydrocephalus at some stage in all, and it is regarded as the most constant component of this syndrome. The median aperture of the fourth ventricle is most probably closed early in foraminal impaction, or if not closed it communicates directly with the spinal subarachnoid space and the return of cerebrospinal fluid to the posterior fossa cisterns is obstructed by the impacted cerebellar tissue. The lateral apertures of the fourth ventricle are sealed later and less adequately by compression between the flocculus and the cerebellar tissue, caudal to the flocculus, as these structures are pressed against the floor of the skull.

Sustained hydrocephalus is responsible for the flattening of the convolutions at autopsy and the downward movement of the mid-brain with upper brain-stem compression. The clinical features and the autopsy

findings in the fourth patient showed that this process was actually responsible for his death. The ptosis, loss of upward gaze, extensor rigidity and tachypnœa with congested œdematous lungs cannot easily be attributed to medullary compression. Magnus (1924) showed in animals that decerebrate rigidity produced by a cut through the mid-brain, is lost after a cut below the vestibular nuclei, and the same sort of lesions seem to produce decerebrate or extensor rigidity in man. It is difficult to be sure that upper brain-stem compression played no part in the illness of other patients. In addition, the hydrocephalus is responsible for the frontal headache which so dominated the illness of the first patient. The slow-wave focus in the fourth patient and the hypersynchronous discharges in the electroencephalogram in the first are a product of cortical compression from hydrocephalus. Though the white matter is much more vulnerable to compression in hydrocephalus, or to any other compressing lesion, extensive damage to nerve cells in the cortex has been encountered in a patient with hydrocephalus, whose brain has been examined in this laboratory. It is therefore not surprising that acute hydrocephalus may produce a sort of cerebral tamponade with slow-wave foci or epileptic discharges from the cortex. It is this phenomenon which accounts for the rare focal cortical seizures, usually with convulsive movement spreading from the face to hand, described by Collier (1904) in cerebellar tumours. In addition to the upper brain-stem compression, headache and electroencephalographic findings of hydrocephalus it also increases the degree of foraminal impaction, by enlarging the size of the brain and pushing the brain-stem downwards.

However, the most characteristic features of this form of hydrocephalus are the way it fluctuates in intensity, and the clinical episodes known as hydrocephalic attacks caused by these fluctuations. A minor degree of brain swelling presses the flocculus and inferior surface of the cerebellar hemispheres more firmly against the floor of the skull. This renders the partial seal of the lateral apertures of the fourth ventricle complete. Cerebrospinal fluid secretion continues, dilating the ventricular system still further and so expanding the brain and increasing the degree of foraminal impaction. Venous hæmorrhages found under the ependyma of the fourth ventricle in Case 2 suggest a very steep rise in intraventricular pressure as they are very similar in character to the venous hæmorrhages so commonly found in the wall of the hæmatoma cavity of the more acute cases of massive cerebral hæmorrhage. Slight venous obstruction early in the hydrocephalic attack may cause faster secretion of the cerebrospinal fluid, but later the pressure in the ventricles may reach a height adequate to arrest secretion from the choroid plexus and allow the hydrocephalus to subside. Hydrocephalic attacks may be arrested by tapping the ventricles, and prevented by ventricular drainage, so long as it functions.

XUM

The clinical manifestations of the hydrocephalic attack develop over a few seconds. Most commonly agonizing frontal or suboccipital and high cervical pain, or all three, usher in the attack. It may consist of pain only, as in the first patient, when it is commonly referred to as hydrocephalic headache; or the pain may be followed by any of the manifestations of the foraminal impaction which have already been described. In the first patient hydrocephalic headaches were the prelude to sudden death. In the second coma, respiratory arrest and residual quadriplegia came on in this manner. The third showed two attacks of coma and respiratory arrest, the first attack leaving a residual quadriplegia. In the fourth patient a hydrocephalic attack caused fatal upper brain-stem compression. The fifth patient had only one attack, manifested by deafness and coma. In the sixth the sudden onset of a confusional state may have been such an attack. This patient also had hydrocephalic headaches as a prelude to the sudden death. The attack often leaves the patient in no condition to report the presence of headache at the onset. If it consists of headache only it may last only a minute or two and rarely more than ten minutes, but its severity exceeds that of any other form of headache, including subarachnoid hæmorrhage. Transitory confusion, deafness or blindness during the headache is common. The hydrocephalic attack is the hallmark of foraminal impaction, but other forms of hydrocephalus, particularly that complicating tumours within the third ventricle, may be associated with hydrocephalic attacks. A similar attack with sudden agonizing headache followed by coma, arrest of respiration and extensor rigidity has been produced by an inexperienced neurological surgeon who pumped air vigorously into the ventricles through a brain needle, while omitting to allow any cerebrospinal fluid to escape. The patient recovered promptly when the syringe was removed and the cerebrospinal fluid squirted out in a jet. The coma appeared to be a product of upper brain-stem compression and there was no evidence of foraminal impaction.

Effects of Neck Movement

Several patients have been seen with the clinical syndrome of foraminal impaction, whose brains have not been examined at autopsy. In some of these, neck flexion has been noted to arrest respiration and normal breathing has returned promptly when the neck was extended again. However, this phenomenon has been noted in patients who appeared to be suffering from upper brain-stem compression and its exact significance is not yet understood.

Diagnosis of Foraminal Impaction

The most constant feature of this syndrome is the hydrocephalic attack, and in early cases specifically its mildest form, the brief agonizing pain of hydrocephalic headache with or without transitory confusion,

deafness or amaurosis. Inconstant features are bilateral cranial nerve palsies from seven to ten inclusive, neck rigidity and sustained hydrocephalus, developing insidiously. There has been no definite evidence of medullary compression except as a catastrophic result of a hydrocephalic attack. Between attacks the patients are usually alert in contrast to the insidious progressive global impairment of consciousness characteristic of upper brain-stem compression. Extensor rigidity, loss of pupillary light reflexes and rapid deep respiration are manifestations of upper brain-stem compression, but they may be seen in foraminal impaction if upper brain-stem compression complicates a hydrocephalic attack. None of these patients showed erosion of the sella turcica in skull X-rays. Papillœdema was either absent or minimal, developing in the last hours of life. The series is too small to draw conclusions from these two observations, but if the mechanism of erosion of the sella turcica suggested in the first part of this paper is correct, it is a sign of early upper brain-stem compression.

Basilar invagination is a condition which is never likely to be mistaken for foraminal impaction, but it has a great deal in common with it. In this disease the foramen magnum is slowly forced upwards into the skull as a result of weakness of bone, such as may occur in Paget's disease and osteogenesis imperfecta. The foramen magnum is narrowed and the undersurface of the cerebellum and medulla oblongata are impacted within the foramen magnum. In basilar invagination O'Connell and Turner (1950) reported neck pain, hydrocephalus, interference with the function of the lower cranial nerves from five to twelve inclusive and milder and insidious signs of medullary compression. They noted slow, shallow respirations in their second case with dramatic return to normal after a posterior fossa decompression. Spillane, Pallis and Jones (1957) also noted a vertical nystagmus very similar to that seen in the second patient and a liability to quadriplegia following trivial trauma. In basilar invagination the anterior part of the rim of the foramen magnum moves upwards more than the posterior part and this may account for the absence of hydrocephalic attacks. In a recent example the odontoid process compressed and indented the medullary pyramids.

The Cause of Foraminal Impaction

This syndrome is much less common than upper brain-stem compression, even allowing for the possibility that examples have been overlooked in this series. 1 patient in 6 shows no herniation of cerebellar tissue below the foramen magnum and it is suspected that these patients would never develop foraminal impaction under any condition. 5 normal patients out of 6 have some degree of what Spillane, Pallis and Jones (1957) call cerebellar ectopia and it is probable that cases of foraminal impaction are only recruited from the more severe examples of this

XUM

condition. Several fatal cases of cerebellar metastatic tumour and hæmorrhage have been seen without any herniation of cerebellar tissue below the rim of the foramen magnum. As Cushing observed (1917), tumours of the cerebellar hemispheres increase the degree of cerebellar ectopia while tumours of the cerebellopontine angle do not. In this series the acoustic neuroma was most unusual in that it had burrowed into the cerebellar hemispheres. Cairns (1949) mentions foraminal impaction as a complication of meningitis and 2 of these patients suffered from generalized brain swelling secondary to meningitis. Therefore it is not possible to state whether a patient will or will not have foraminal impaction because his space-occupying lesion is placed in one place and not another, any more than it is possible to forecast whether he will or will not suffer from temporal lobe herniation. It is natural to suspect that a mild degree of basilar invagination would predispose to foraminal impaction as may the Chiari malformation (Greenfield, 1958). Massive cerebellar swelling may produce impaction alone, but in a few patients downward movement of the brain-stem from any cause may be arrested by this deformity before the dentate ligaments become taut.

Treatment.—A diagnosis of foraminal impaction is an indication for treatment at once, if the disasters recorded in this paper are to be avoided. Tapping the lateral ventricles with a brain needle inserted through a burr hole will arrest an attack, and ventricular drainage, if the ventricles are large, will render the patient safe for a day or two. However a posterior fossa decompression removing the posterior part of the rim of the foramen magnum, the arch of the atlas, wide opening of the dura mater and preferably excision of the herniated tonsils is the most satisfactory procedure, if the cause of the state of raised intracranial tension cannot be removed at once. Hydrocephalic attacks demand immediate treatment even if some other mechanism than foraminal impaction is responsible for them.

Lumbar Puncture in Patients with Raised Intracranial Tension

Though no disaster will follow lumbar puncture, immediately or in a few hours, in 19 patients out of 20, the anatomical variations in the shape of the brain, dura mater and skull, make it impossible to forecast whether hernias of the brain are occluding the tentorial space or foramen magnum. Such impaction, incriminated by Smyth and Henderson (1938) for these disasters, may be more likely in temporal lobe tumours or cystic tumours of the cerebellar hemispheres, but they may be present in such conditions as meningitis or subarachnoid hæmorrhage. Lumbar puncture should therefore only be performed when it is absolutely essential for the proper management of the patient, if raised pressure or a space-occupying lesion within the skull is suspected.

SUMMARY

(1) The clinical and pathological findings in a series of 150 cases of upper brain-stem compression have been reviewed.

(2) In some patients hernias of the temporal lobes compressed and distorted the mid-brain and the clinical syndrome has been described in detail.

(3) In other patients an identical syndrome was found without any significant hernia through the tentorial space. Both groups showed flattening of the convolutions, which is regarded as a sign of downward displacement of the brain-stem.

(4) The mechanism by which the brain-stem is compressed in pure downward displacement of the brain-stem is described.

(5) The importance of anatomical variations in determining the pattern of brain-stem compression is emphasized.

(6) The nature of the vascular lesions seen in brain-stem compression and the problem of irreversible compression are discussed.

(7) The anatomical deformity of foraminal impaction is defined.

(8) The case histories of 6 patients showing this deformity are given.

(9) The clinical syndrome of foraminal impaction is described and the importance of hydrocephalic attacks is stressed.

(10) Notes on the diagnosis, comparison with basilar invagination, treatment and risk of lumbar puncture are included.

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ACKNOWLEDGMENT

I wish to express my gratitude to Miss E. A. Sweezey for the diagrams; to the departments of medical illustration at the Montreal General Hospital and the Queen Mary Veterans' Hospital in Montreal for the photographs; to Dr. J. E. Pritchard, Dr. W. H. Mathews and Dr. Hugh Starkey for facilities to carry out this work in the pathology departments of the Montreal General Hospital and the Queen Mary Veterans' Hospital; to the Physicians and Surgeons who have allowed me to report their cases, and to the Canadian Life Officers' Association and the Department of Veterans' Affairs who supported this work financially, as part of an investigation into the pathology of cerebral vascular disease.

ILLUSTRATIONS FOR PLATES

PLATE XLII

FIG. 3A.—Sagittal section of the brain 8 mm. from the mid-line in a patient with massive cerebral hæmorrhage in the other hemisphere. The angulation of the brain-stem is well shown. The small anterior and posterior temporal lobe hernias are probably of only slight significance.

FIG. 3B.—Dissection of a normal brain-stem and thalamus viewed from behind. The close relationship of the pulvinar to the temporal lobe is shown.

FIG. 3C.—Assymmetrical compression of the tectum and tegmentum of the mid-brain by a massive cerebral hæmorrhage. There was no compression of the mid-brain by temporal lobe hernias in this patient but hernia of the cingulum under the falx cerebri added to the distortion of the mid-brain.

PLATE XLIII

FIG. 3D.—Symmetrical compression of the tectum and tegmentum of the mid-brain in a patient with hæmorrhage, confined to the subarachnoid space, from a ruptured berry aneurysm arising from the junction of the left internal carotid artery and the posterior communication artery. Some of the territories of both middle cerebral arteries and the left anterior cerebral artery were infarcted. There was no temporal lobe herniation. The convolutions are not flattened because of treatment with hypothermia.

FIG. 4.—Sagittal section of the brain-stem and cerebellum of Case 3 showing infarction of the medulla.

FIG. 5.—The cerebellar deformation in Case 6. The unusual prominence of the flocculus is shown by arrows.

PLATE XLII

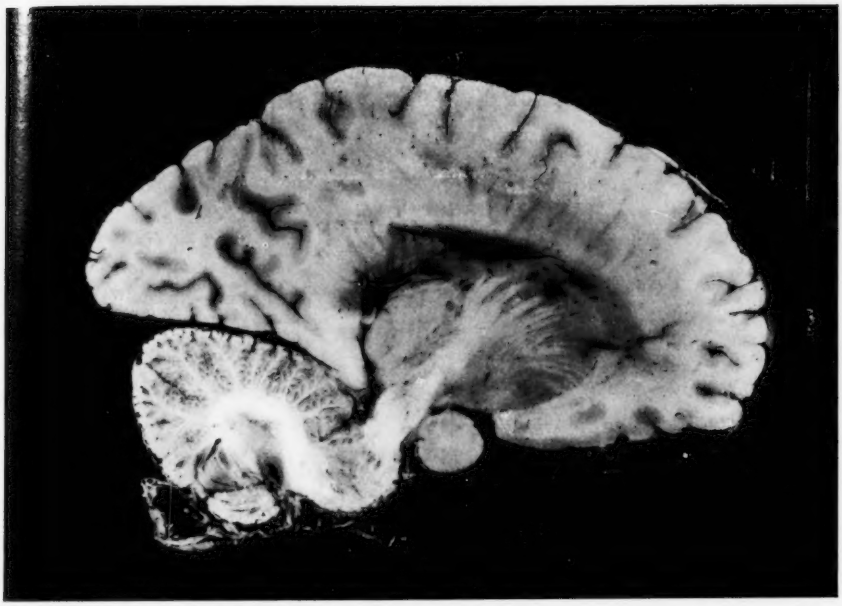

FIG. 3A.

FIG. 3B.

FIG. 3C.

To illustrate article by D. A. Howell.

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PLATE XLIII

FIG. 3D.

FIG. 5.

FIG. 4.

To illustrate article by D. A. Howell.

SOME APPLICATIONS OF THE URINARY PHENOLSULPHONPHTHALEIN EXCRETION TEST IN HYDROCEPHALUS AND RELATED CONDITIONS

BY

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A QUANTITATIVE urinary excretion test, using phenol red, was first introduced by Dandy and Blackfan in 1914 and 1917, who showed that the amount of dye excreted in the urine up to two hours after its injection into the lateral ventricle or lumbar theca, is less in hydrocephalic infants than in infants with a normal cerebrospinal fluid pathway. This observation was based on a small series of 26 hydrocephalic patients, in only 15 of whom the anatomical site of the blockage was known. The excretion results were roughly classified into two groups, those with or without a direct communication between the lateral ventricles and the lumbar theca. Later, Ingraham and Matson (1954) published an elaborate method of this type of investigation, the results of which were difficult to interpret.

The present study of the urinary phenol-red excretion test, initiated by Dr. A. L. Woolf, was undertaken to develop this, and explore its prognostic value in hydrocephalus and related conditions.

Material.—Three hundred and thirty tests were carried out on 205 patients attending The Hospital for Sick Children and the Westminster Children's Hospital, London. In all cases the anatomical site of the block was ascertained either from satisfactory pneumo-encephalography or careful post-mortem examination, using a specialized technique described by Laurence and Martin (1959). The composition of the series, shown in Tables I and II, includes many cases of spina bifida cystica often associated with hydrocephalus, as a special study was made of this problem.

Method.—The method, modified from Dandy and Blackfan's, has been fully described in a preliminary communication (Laurence, 1957), and will only be outlined here.

3 mg. of phenolsulphonphthalein (phenol red)[2] accurately neutralized just before

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[2]Supplied in ampoules containing 6 mg. of dye in alkali by Savory and Moore, 143 New Bond Street, London, W.1.

XUM

TABLE I.—PHYSIOLOGICAL SUBDIVISION
(310 tests on 190 patients)

	Number of tests		
	Intraventricular	*Intrathecal*	*Number of patients*
Communicating	74	132	124
Non-communicating ..	62	42	66
	136	174	190

TABLE II.—ANATOMICAL SUBDIVISION
(330 tests on 205 patients)

	Number of tests		
	Intraventricular	*Intrathecal*	*Number of patients*
Normal	7	13	15
Basal cistern block ..	46	51	58
Intraventricular block ..	24	17	30
Intraventricular and basal cistern block	16	16	17
Spina bifida cystica ..	48	88	83
Over-secretion	2	2	2
	143	187	205

use, are injected into the lateral ventricle or the lumbar theca. All urine passed during the next twenty-four hours is collected in divided specimens at one, two, four, six, nine, twelve, eighteen and twenty-four hours after injection of the dye.

Each specimen is rendered alkaline with an excess of 10 per cent sodium hydroxide (and thus turns pink if it contains phenol red), and the total volume is then noted. About 10 ml. are centrifuged and the colour intensity of the supernatant is estimated photo-electrically with an Ilford 604 filter, using centrifuged, alkaline urine as a blank, and a phenol-red solution as a standard. The phenol-red content of each specimen is then only a matter of simple calculation. The amount of dye excreted in the first six hours is worked out and expressed as a percentage of the total injected. It is advisable to draw a histogram to assist in the interpretation.

The absorption of dye from the cerebrospinal fluid pathway into the blood vessels and its subsequent excretion in the urine should be a smooth process, however slow that may be in the presence of an abnormality of the third circulation. In infants and young children, however, urine production may be completely suppressed for one to two hours, or even longer, following catheterization or pain such as the simple needle prick of the dye injection (Smith, 1951; Vesterdal and Tudvad, 1949; Wilkinson, 1958). This is one of the reasons why a six-hour excretion value is preferable to the two-hour value used by Dandy and Blackfan. Extra fluids may be given by mouth to stimulate urine production, before and during the test, but intravenous or subcutaneous fluids for this reason alone are considered unjustifiable. At the end of the six-hour period the bladder may be emptied by applying gentle pressure over the lower abdomen.

When dye excretion is erratic something has usually gone wrong with the test. This may be due to suppressed urine production for reasons just mentioned, to anæsthetics, which should be avoided, or leakage of the cerebrospinal fluid into the tissues. Dehydration and vomiting will, of course, also reduce urine output. On the other hand urine collection may have been faulty. The last reason alone makes it essential to have the full co-operation of the ward staff. With infants, a collecting

device such as Paul's tubing for males and a catheter for females is recommended for recovery of the total urinary output. Accidental losses must be reported accurately; soiled napkins and sheets should be kept, for it is sometimes possible to estimate the amount of dye lost from the size of the wet patch, and the intensity of the pink colour after exposure to ammonia fumes.

Where there is a raised fontanelle tension, lumbar puncture for the lumbar dye test may be dangerous and lead to errors. Coning might be precipitated in the presence of intraventricular block, while sometimes prolonged leakage into the tissues of cerebrospinal fluid and dye through the puncture in the meninges causes the dye to be excreted too rapidly. To reduce the cerebrospinal fluid pressure some cerebrospinal fluid should be withdrawn by a ventricular puncture.

It is advisable to continue the test for twenty-four hours rather than for the minimum of six hours, so that these errors may be detected. The histogram is of particular value here for it soon illustrates irregularities in the dye excretion.

When there is active inflammation of the cerebrospinal fluid pathway, the test should not be performed, as the dye absorption may be completely upset and the inflammatory process aggravated.

The children tolerate dye injection reasonably well, especially into the lubar theca. Reactions have occurred, usually in the form of a transient pyrexia, and all 5 cases of serious reactions, 3 of chemical meningitis, 1 of cortical vein and sinus thrombosis and 1 sudden death, followed intraventricular dye injection. For this reason and because they are less informative, ventricular dye injections were only carried out in a limited number of cases towards the end of the investigation. The number and severity of reactions, however, compare favourably with those following air studies on hydrocephalic children, who are well known to be easily upset by any form of interference, and especially by ventricular tapping, Pennybacker (1953).

Results

Although full information is only obtained from results of both intraventricular and intrathecal injections, the former are not always justifiable in view of the increased risk of reactions (fig. 1).

Normal cerebrospinal fluid pathway.—As most of the patients investigated were thought to be hydrocephalic, only a few children fall into this group. After intrathecal injection, at least 40 per cent of the injected dye is excreted, while in most cases following its intraventricular injection, only about 25 per cent of the dye is recovered within six hours. This difference is probably explained by two factors. Firstly, dye injected into a lateral ventricle is considerably diluted, even in a normal ventricular system, whereas little or no dilution takes place when injected into the theca. Secondly, the cerebrospinal fluid containing phenol red has to pass out into the subarachnoid space before absorption occurs.

Basal cistern block.—This lesion is invariably inflammatory and usually follows perinatal "trauma" or a meningeal infection. In some cases there may be no evidence, clinical or even histological, to suggest which of these two was the likely ætiology. In both instances the meninges in the posterior cranial fossa are thickened and the cerebrospinal fluid pathway is occluded, allowing cerebrospinal fluid to reach the subarachnoid space,

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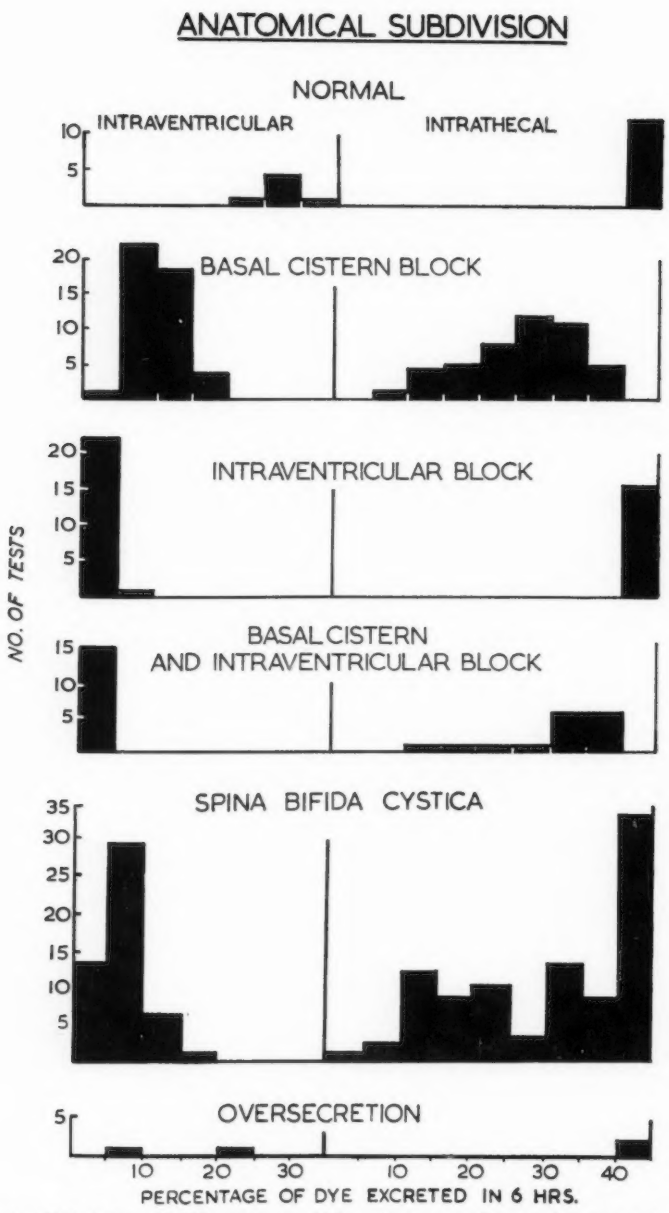

FIG. 1.—Tabulation of 330 results on 205 patients according to the anatomical site of the block. The amount of dye excreted in six hours is plotted horizontally, the number of tests in each 5 per cent dye excretion group vertically. The ventricular dye excretion results are on the left, the thecal on the right.

but preventing it from passing beyond the basal cisterns to reach the main absorptive area over the cerebral hemispheres.

The results, both after intrathecal and intraventricular injection, are below normal, but practically always above 5 per cent. In one case where there was very gross dilatation of the lateral ventricles, the ventricular dye excretion result was only 3·5 per cent. The excretion values after intrathecal injection show a relationship to the level of the block within the

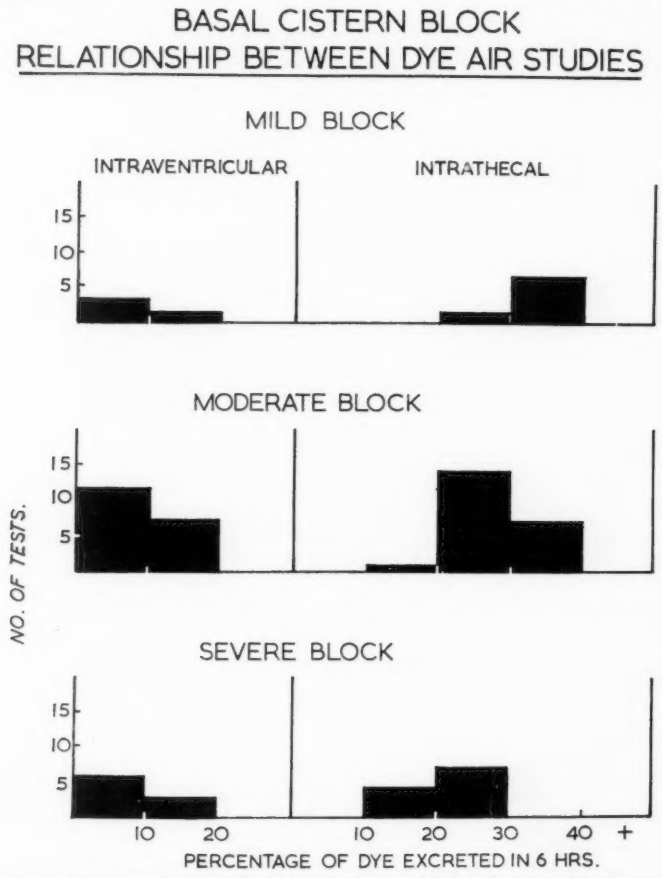

FIG. 2.—Tabulation of 67 results on 39 patients with basal cistern block, according to the level of the block determined by air studies or at autopsy. *Mild:* at cisterna ambiens and chiasmaticus. *Moderate:* at cisterna interpeduncularis. *Severe:* at cisterna magna or pontis.

The amount excreted in six hours is plotted horizontally, the number of tests in each 10 per cent dye excretion group vertically. The ventricular dye excretion results are on the left, the thecal on the right.

basal cisterns, which has been ascertained either by accurate ventriculography, or later, at post-mortem, by special techniques. The more distal the block within the cisterns, the higher the excretion value seems to be (fig. 2). A similar correlation exists between the thecal dye excretion results and prognosis. In the cases in which the course of the disease has not been altered by surgery, a higher excretion result seems to indicate a more hopeful outcome (fig. 3).

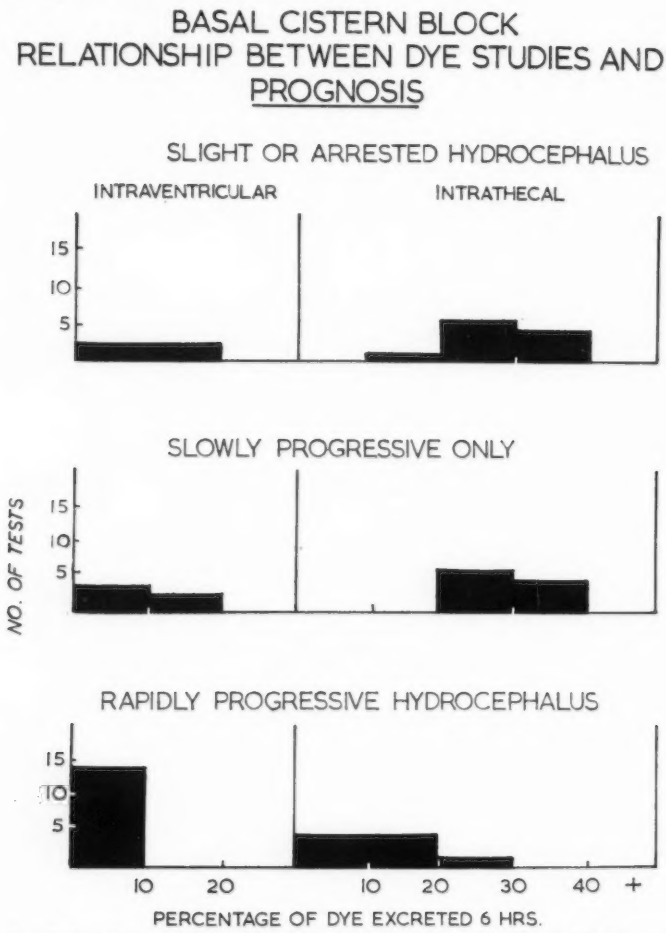

FIG. 3.—Tabulation of 57 results on 28 patients with basal cistern block, according to prognosis. In these the course of the disease was not altered by surgery. The amount excreted in six hours is plotted horizontally, the number of tests in each 10 per cent dye excretion group vertically. The ventricular dye excretion results are on the left, the thecal on the right.

The results, after intraventricular injection of dye, show no correlation with either prognosis or the level of the block within the basal cisterns. Indeed, the results seem to be more an index of the degree of ventricular dilation, and so also of the dilution of the dye and of stasis of the cerebrospinal fluid.

Intraventricular block.—This is a small but important group of cases where dye, injected into the lateral ventricle, is prevented from leaving the ventricular system and from entering the subarachnoid space, where it could then be absorbed normally. In all but one instance excretion values after ventricular dye injection were below 5 per cent, and frequently 1 per cent or less, and the dye continued to be excreted in the urine in small amounts for long periods. In that one case, which had an excretion value of 8 per cent at ventriculography a little air was found to pass, through the partially blocked aqueduct, into the fourth ventricle and the basal cisterns.

It is clearly not possible to locate the actual site of the intraventricular block by this method, but by means of an intrathecal dye test, it is possible to separate the cases with normal subarachnoid pathways from those which have basal cistern block in addition. In the former, where the block is generally in the aqueduct and is usually a malformation, the excretion values fall within the normal range. In the latter group, with a basal cistern block in addition, generally post-inflammatory, the thecal dye excretion results are the same as in those which have a basal cistern block alone.

Spina bifida cystica.—The cases of spina bifida cystica form a large group with wide variations in excretion values. A small proportion of these did not have hydrocephalus, but in the others the hydrocephalus has been caused by a variety of lesions. Congenital malformations of the aqueduct or of the hind-brain (the Arnold-Chiari malformation) may in themselves give rise to hydrocephalus (Laurence, 1959*b*), but ascending infection from the spina bifida sac, which is generally unepithelialized at birth, may lead to any one of a number of superimposed inflammatory lesions. Any combination of lesions, congenital or acquired, may be found in a particular case, accounting for the very variable excretion results. It is thus difficult from the amount of dye excreted to deduce the site of the block.

The excretion results, however, may be used as an aid to prognosis. It was found that the majority of cases with low lumbar dye excretion were those in which a hydrocephalus progressed to a fatal outcome unless the disease was surgically arrested, while the bulk of children with high excretions were those without hydrocephalus or those in whom the disease had arrested before the test (fig. 4). In this group, the ventricular dye results are little more than an index of ventricular dilatation.

Most of these results refer to children over 3 months old, generally admitted to hospital for treatment of their spina bifida cystica or for hydrocephalus. At that age 78 per cent of children with spina bifida cystica who develop hydrocephalus have already obvious manifestations

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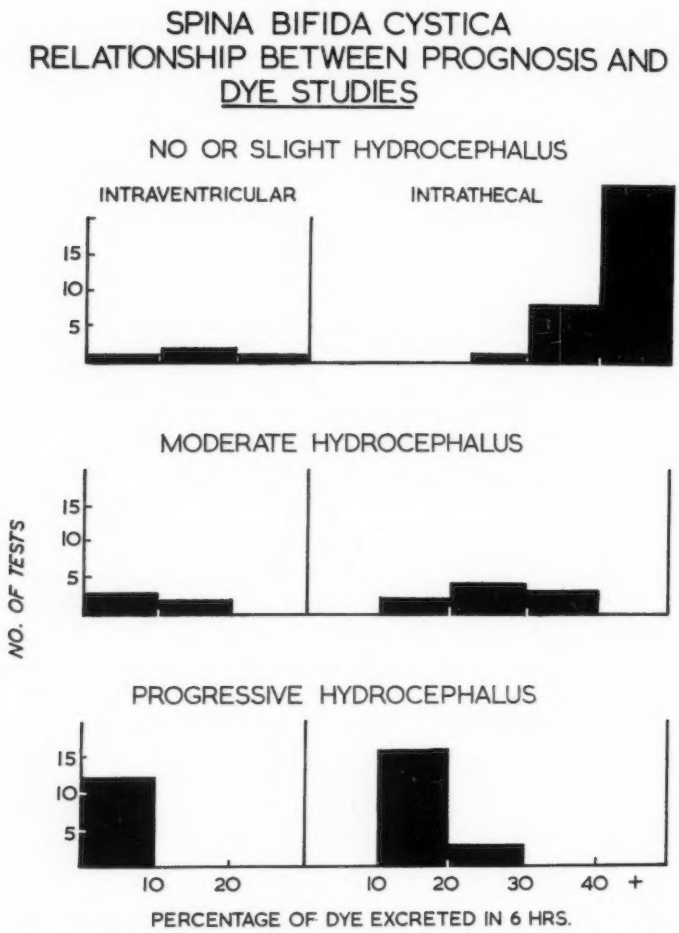

FIG. 4.—Tabulation of 83 results on 47 patients with spina bifida cystica, according to the clinical course. The amount excreted in six hours is plotted horizontally, the number of tests in each 10 per cent dye excretion group vertically. The ventricular dye excretion results are on the left, the thecal on the right.

of it (Laurence, 1959*a*). In order to try to apply this test at the stage when the clinician is often first asked to give a prognosis, 12 infants under the age of 10 days, without obvious clinical hydrocephalus, were tested and followed up to see whether they developed head enlargement. It must be borne in mind that a neonate with a high excretion value, and therefore presumably reasonable cerebrospinal fluid circulation, may well sub-

sequently develop an obstructive lesion resulting from an ascending infection. So it is possible to indicate only those infants who are unlikely to escape progressive hydrocephalus. This is confirmed by the results (fig. 5), for not only are the 2 infants with low excretion values included in the "rapidly progressive" group, but also 2 with normal or near normal excretion results who subsequently developed meningitis. The investigation of such children in the neonatal period, however, is far from easy, as

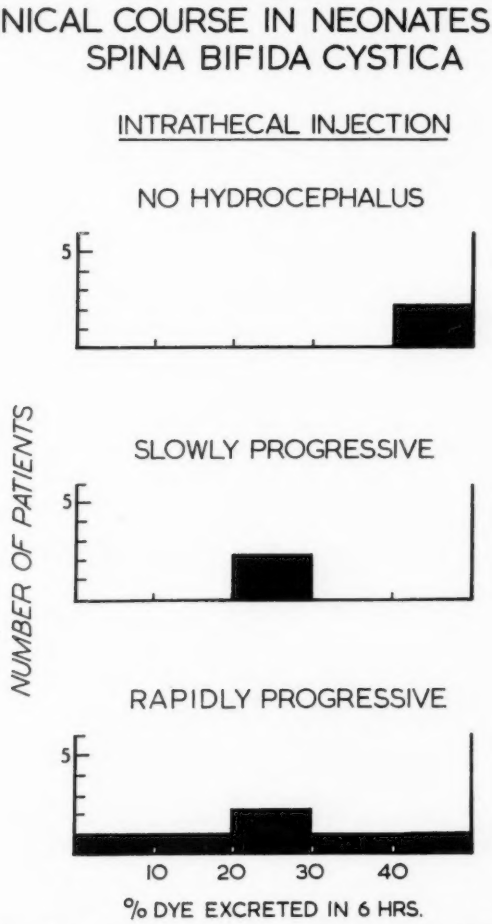

FIG. 5.—Tabulation of lumbar dye injection results according to prognosis, in 12 patients with spina bifida cystica, under 10 days of age. The amount of dye excreted in six hours is plotted horizontally. The number of tests in each 10 per cent group is represented vertically.

the lumbar puncture is difficult, sometimes hazardous, and urine collection troublesome. It is doubtful, therefore, whether this particular use of the test is really practicable.

The development of hydrocephalus sometimes follows the excision of a spina bifida cystica. Dandy and Blackfan (1914), Penfield and Cone (1932) and others suggested that this was due to the removal of an important, often indispensable, cerebrospinal fluid absorptive surface, which acts as a compensatory mechanism. This particular point was investigated by means of pre- and post-operative intrathecal dye excretion estimations in 16 patients (fig. 6). If it is accepted that the experimental error of the test is in the order of plus or minus 5 per cent, then the majority of cases had identical pre- and post-operative results. Only 6 cases had

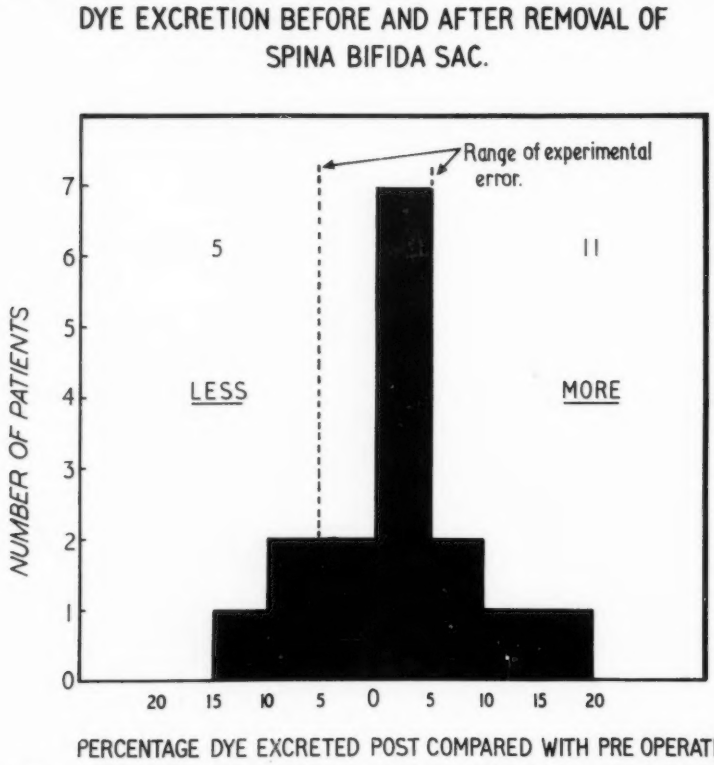

FIG. 6.—Comparison of thecal dye excretion results before and after surgical removal of the sac in 16 cases of spina bifida cystica. The results are expressed as the difference between the values; reduced excretion to the left of zero, increased to the right; while the number of patients in each group is represented by the size of the columns.

excretion values outside these limits and in only 1 case was there a significant reduction, while in 2 there was a significant increase in the post-operative dye excretion values. These results suggest that the removal of the spina bifida sac does not interfere with the absorption, and the sac probably has no cerebrospinal fluid absorptive powers. This is not surprising as the sac is frequently loculated and the loculi are not often in communication with the spinal subarachnoid space by the time surgery is undertaken.

When a post-operative hydrocephalus is precipitated, this is probably due to bleeding or spilling of operative debris into the subarachnoid space, an operative infection of the cerebrospinal fluid as has been suggested long ago by Muscatello (1902) or an upset in the internal equilibrium resulting from cerebrospinal fluid loss or leakage. All these factors are known to aggravate an existing or an incipient hydrocephalus.

Over-secretion.—Two cases were tested which, clinically, had over-secretion of cerebrospinal fluid. Both had marked dilatation of the ventricular system, while air studies demonstrated that air passed from the basal cisterns into the Sylvian fissures. One of these was an example of choroid plexus hypertrophy. While ventricular dye results were low, a reflection of the ventricular dilatation, in both instances dye excretion after lumbar injection was rapid and high (76 per cent and 61 per cent). This suggests that dye, and possibly cerebrospinal fluid absorption also, are markedly increased in these cases.

"*Subdural Dye Test*".—This test, where dye is injected into the subdural space, was originally designed to select patients for a form of ventriculo-subdural anastomosis, and was described in detail elsewhere by Forrest, Laurence and Macnab (1957*b*). Eighty-six such tests were carried out on 78 patients. In normal cases phenol red was absorbed rapidly from the subdural space, and more than 50 per cent of the injected dye was excreted in the urine within six hours.

In 3 cases of subdural hæmatoma extremely low excretion values were obtained (less than 5 per cent) while results ranging from 5–30 per cent were recorded in 9 cases, with a subdural collection of clear, serous fluid. Variable, but generally subnormal, amounts were excreted in cases of hydrocephalus following meningitis, and less commonly of birth hæmorrhage.

Discussion

On the basis of experiments using dogs, Dandy and Blackfan (1914) and Frazier and Peet (1914), working independently, showed that cerebrospinal fluid was not reabsorbed in the ventricles, but by the whole arachnoid, and that in cases of hydrocephalus, reduced urinary dye excretion values reflected the reduction in the available absorptive area. Although their values were consistently higher, the present investigation

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confirms most of their assumptions. Nevertheless, at least some of the phenol red must be absorbed from the ventricular system, as in cases of complete intraventricular block, anything up to 5 per cent of the injected dye is excreted within six hours. This may be due to the fact that in cases of hydrocephalus, most of the ependymal lining of the ventricles is denuded, possibly thereby resulting in abnormal conditions. Davson (1956) suggests that the ependyma offers little impediment to the passage of phenolsulphonphthalein from the ventricle into the brain parenchyma. There, it is retained probably both in the extracellular fluid and in the cells, as it cannot easily pass the blood-brain barrier from there into the blood capillaries. This would account, not only for this slight urinary excretion of dye in the presence of complete intraventricular block, but also for the finding that the total amount of dye is never completely recovered from the urine within the twenty-four hours, even in a normal ventricular system.

Dandy and Blackfan were at a disadvantage in classifying their cases for their earlier paper in 1914, as air encephalography, now essential in diagnosis, was not introduced by Heuer and Dandy until 1916. They depended on a simple dye test to divide their cases into communicating and non-communicating types. As overlapping of the dye excretion results occurred, it was considered that a third group with a partial communication must exist. Similar overlapping occurs when the results of the present investigation are tabulated according to the presence or absence of communication (fig. 7), but when the results are classified according to the anatomical site of the block, clear-cut groups with distinct dye excretion patterns emerge. Conversely, it is possible from the dye excretion value to deduce the site of the block in a particular case (fig. 1).

The chief value of the test is that it is simple and requires no special apparatus. It is a satisfactory ancillary investigation, which can be used to confirm results obtained by complete and exhaustive air encephalography, but the test is not intended and cannot be expected to replace the latter. When air studies are not entirely reliable it may indicate the position or a blockage in the cerebrospinal fluid pathway, and it also helps in assessing the prognosis of hydrocephalic patients.

These views of the dye excretion test are opposed to those of Behring (1956), who assumed that the excretion result, following intrathecal injection like that after intraventricular injection is only a measure of ventricular dilatation. He based his assumption on the observation of Dandy and Blackfan (1914) who state that dye injected into the lumbar theca appears rapidly in the ventricular cerebrospinal fluid in communicating types. Although such mixing does occur, this usually seems slight when the patient is resting.

This dye excretion test is of great importance when a Torkildsen's ventriculo-cisternostomy is to be performed, for this operation will be

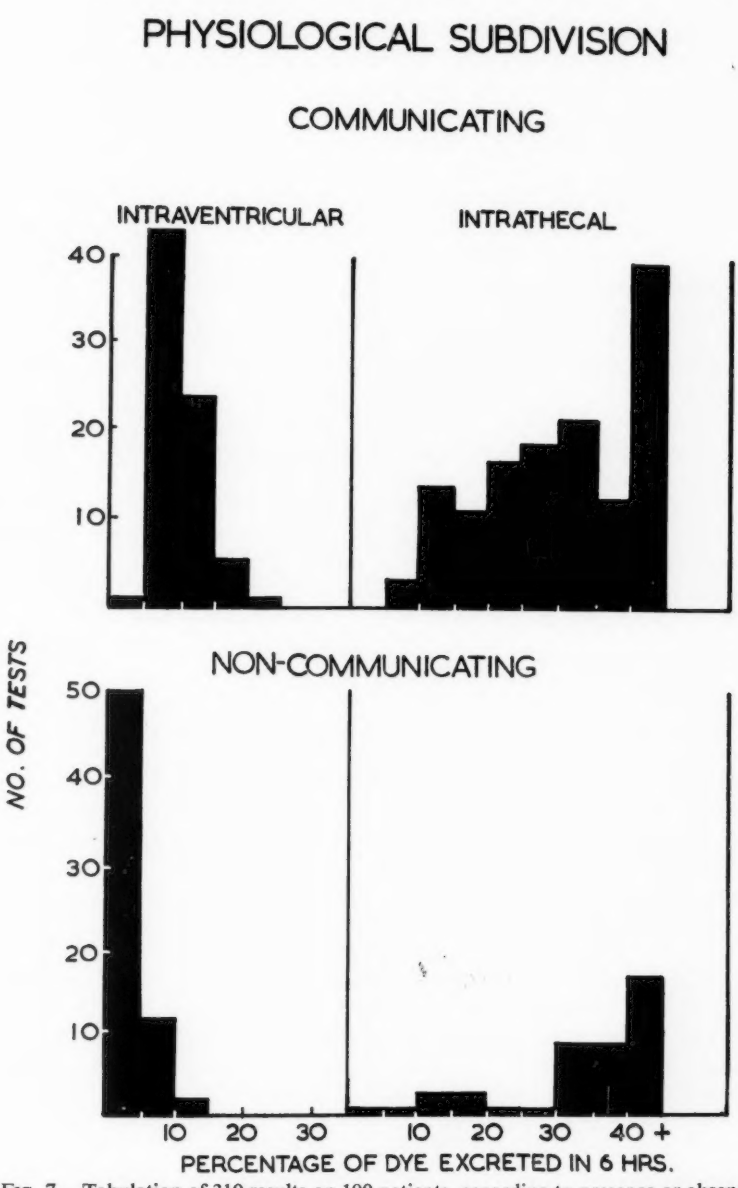

FIG. 7.—Tabulation of 310 results on 190 patients, according to presence or absence of communication, etc. The amount of dye excreted in six hours is plotted horizontally, the number of tests in each 5 per cent dye excretion group vertically. The ventricular dye excretion results are on the left, the thecal on the right.

XUM

unsuccessful when there is a basal cistern block. The dye test will separate cases of aqueduct block with an additional cistern block, from those with a normal subarachnoid space. Thus, a lumbar encephalogram is avoided.

Although the ventriculo-subdural anastomosis (Forrest, Laurence and Macnab, 1956*a*) has now been largely abandoned in favour of more promising procedures, the subdural dye excretion test has yielded some interesting results. These tend to confirm some ideas about the subdural space in pathological conditions as well as to show that fluid may be absorbed from the space.

Summary and Conclusions

A method of carrying out the urinary phenolsulphonphthalein excretion test in hydrocephalus and related conditions, following dye injection into the lateral ventricle and the lumbar theca is described. Precautions necessary for reliable results are discussed in detail, and the results of 330 tests on 205 patients are presented.

(1) When results are divided according to the anatomical site of the lesion, clear-cut groups with distinct dye excretion patterns emerge. Conversely, from the dye excretion values, it is possible to deduce the anatomical site of the block.

(2) The ventricular dye test besides evoking more severe reactions, is only of limited value. The amount of dye excreted is more an expression of the ventricular dilatation than the site of the block, except when this is situated within the ventricular system. Though it is possible to determine whether an intraventricular block is present, its position cannot be located by means of the dye excretion test.

(3) The amount of dye excreted after intrathecal injection is related to the state of the subarachnoid space; in basal cistern block the amount of dye excreted depends largely upon the level of a block within the basal cisterns.

(4) Excretion values following intrathecal injection of phenol red, both in cases of basal cistern block or spina bifida cystica, bear reasonably close relationship to prognosis; those with high excretion values have the best chance of survival. For technical reasons the test was not found applicable to neonates with spina bifida cystica.

(5) The test is an ancillary to exhaustive air encephalography and cannot replace it. It is useful if encephalography is unsatisfactory, and when a Torkildsen's ventriculo-cisternostomy is planned.

Acknowledgments

Thanks are due to Dr. A. L. Woolf who carried out some preliminary studies; to my colleagues at the Westminster Children's Hospital and The Hospital for Sick Children, Great Ormond Street, for their help and

co-operation; to Dr. M. Bodian in whose department this work was largely carried out; to Miss S. Moore and Miss B. Glashier for technical assistance, Mr. J. Lyth for the charts, and the Research Committee of The Hospital for Sick Children for their encouragement and support.

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XUM

EPIDEMIC VERTIGO

Clinical Picture, Epidemiology and Relation to Encephalitis

BY

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A CLINICAL picture with vertigo of sudden onset, usually accompanied by nausea and vomiting, has been described under a variety of names, such as epidemic vertigo, epidemic neurolabyrinthitis and vestibular neuronitis. Later in the course, the vertigo becomes paroxysmal and decreases in severity. Generally, the disease is regarded as benign and is, in most cases, of short duration. The pictures described seem to be closely related, presumably representing the same disease, but it is difficult to assess the literature, because the symptomatology and duration show some variation, and the aetiology is unknown.

During the last ten years or so, numerous epidemics accompanied by vertigo have occurred in Denmark. We know of 25 epidemics comprising about 400 patients, and these represent only a small proportion of the cases. We have made an attempt to analyse the clinical manifestations, the course and the epidemiological background of the disease in these patients. The clinical picture is elucidated below by three different types of epidemics and by the case histories of 16 hospitalized patients.

(1) *Epidemic Dominated by Gastro-intestinal Manifestations*

In a district with a population of about 4,000, an epidemic which was quantitatively characterized by non-neurological symptoms started about the end of October 1956 and continued until the end of February 1957. During the months of January–March 1957, 73 patients, i.e. presumably less than half of the actual number of cases, were examined. The patients were questioned as to symptoms and epidemiological conditions, and a complete neurological and a coarse otological examination with hearing tests and tests for nystagmus, with Bartel's biconvex glasses, were performed. Most of the patients were examined shortly after the onset of the disease, but some months had elapsed in a few cases. Severe cases were presumably more frequent among those examined than among the rest of the patients, of whom we received information from their physicians.

The disease showed its highest incidence in mid-January, at which time 15 cases were recorded within four days.

The age distribution appears from fig. 1; 63 per cent were women and 37 per cent men.

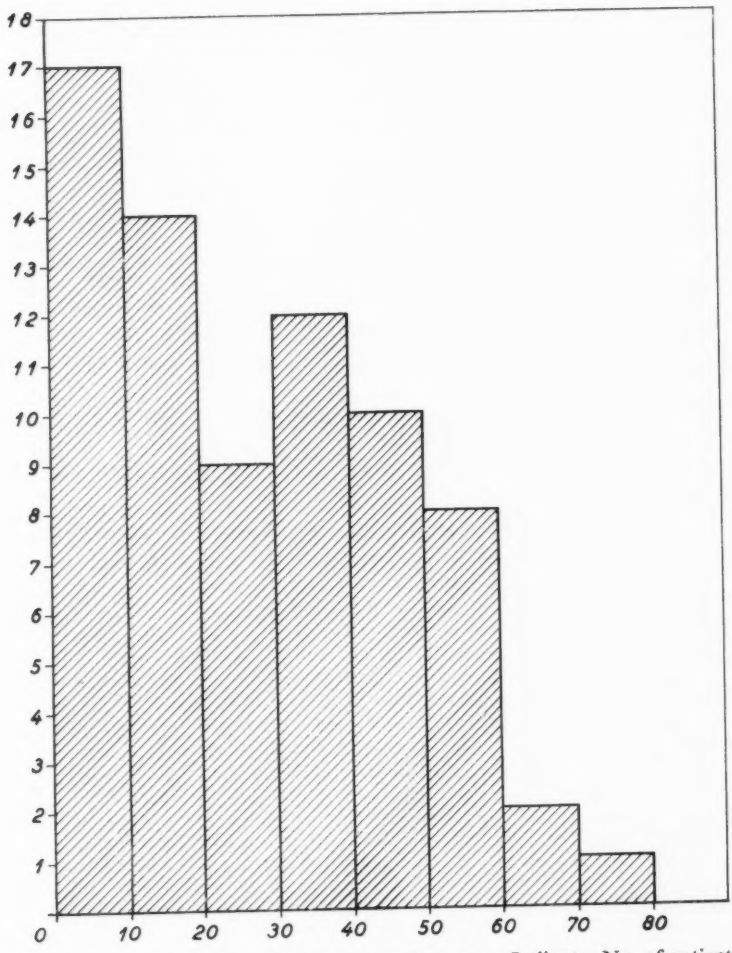

FIG. 1.—Age distribution. Abscissa: Age, in years. Ordinate: No. of patients.

The disease was dominated by non-neurological symptoms, the most common clinical picture being gastro-enteritis with mild vertigo persisting for from a few hours to about two days. In some patients the disease

XUM

began with fever and upper respiratory infection, while vertigo was the initial symptom in a few cases.

Fever was present in 12 patients; nausea in 34, and many of these vomited. Diarrhœa, usually associated with abdominal pain, developed in 36. 3 had thoracic pain unrelated to respiration. A sore throat was present in 2 cases, of which 1 was reminiscent of herpangina. Skin eruptions were not observed. 38 patients complained of vertigo; in 19 it was of only short duration (hours) and so mild that it might be explained as a secondary reaction to the dehydration and intoxication caused by the gastro-intestinal manifestations. In the remaining 19 patients the vertigo was of longer duration and so violent that it was, in most cases, the predominant feature of the clinical picture.[1] Slightly impaired hearing was disclosed in 2 and spontaneous horizontal nystagmus in 6. Apart from those stated in the case-reports, no neurological manifestations were revealed.

Questioning as to contacts between individual patients and, in particular, with relatives in other parts of the country gave information suggesting that the disease could be transmitted by carriers, and that the incubation period was one to two days.

Special neurological interest attaches to the disease not only because of the cases with pronounced vertigo, but also because at least 2 unquestionable cases of acute encephalitis occurred within the district affected by the epidemic.

The various degrees of the disease are illustrated below by 4 case histories from the epidemic; 3 of the patients concerned were admitted to hospital for further investigation.

Case 1.—A girl, aged 15, was admitted to hospital for two days (February 8–9). A week before admission she had had abdominal pain and had vomited once. She had to stay in bed for two days because of fatigue; vertigo was present for five days. She had no symptoms on admission. No neurological abnormalities were revealed. Spinal fluid: pressure 180 mm. H_2O; normal composition. W.B.C. 8,480, with 24 per cent atypical cells. The EEG was markedly abnormal, but as the patient suffered from epilepsy, this was irrelevant to the present illness.

Case 2.—A man, aged 51, was examined on February 28, 1957. His past history was that of good health. He had fallen ill twenty-six days previously, with gyratory vertigo, nausea and epigastric pain, but diarrhœa, fever and upper respiratory infection were absent. He had been confined to bed for ten days because of the vertigo, which was aggravated on movements of the head or eyes. After a fortnight, the vertigo eased and was then present as brief paroxysms, which were provoked especially by movements of the head. The examination revealed a coarse horizontal nystagmus, but no other abnormalities. At a follow-up examination eighteen months later, the patient stated that the vertigo had not disappeared completely until after the lapse of four months.

[1]Vertigo is here used as a term including all sensations of dysequilibrium.

Case 3.—A woman, aged 32, was admitted to hospital from March 5 to March 22, 1957. She had previously been in good health. Three weeks before admission, vertigo suggestive of seasickness had developed. It was aggravated on stooping and on movements of the head, but eased when the patient lay down. A week later, upper respiratory infection occurred. At the same time, she felt as if the left eye turned inwards, and diplopia on left lateral gaze was present. On admission, the ocular symptoms had subsided almost entirely, whereas slight vertigo and fatigue persisted. Slight limitation of ocular movements with a coarse nystagmus, especially on lateral gaze, was observed. Otological examination showed normal auditory and vestibular functions. No neurological abnormalities were disclosed. Spinal fluid: pressure 200 mm. H_2O; 12/3 mononuclear cells; normal protein values. W.B.C. 8,360, with 7 per cent atypical cells. Bone-marrow normal; EEG normal.

At a follow-up examination three months later, the patient stated that the vertigo and diplopia had subsided after six weeks; the fatigue persisted somewhat longer, but had now disappeared.

Case 4.—A man, aged 29, was admitted to hospital from March 7 to March 23, 1957. He had previously been in good health. A fortnight before admission, upper respiratory infection developed, followed about ten days later by a tingling sensation in the left arm and leg and by a right-sided throbbing headache. During the last two days before admission diplopia, especially on right lateral gaze, slightly impaired hearing in the left ear and a staggering gait were noticed. Ophthalmological examination revealed abducens paralysis, but otherwise normal conditions. Otological examination showed slight impairment of hearing in the left ear for high frequencies and a more vigorous caloric response on the right than on the left side. A week later, the hearing was normal, but the caloric test showed directional preponderance to the left. Mild right-sided ataxia and an atypical left plantar response were observed. Spinal fluid: pressure 190 mm. H_2O; 20/3 mononuclear cells; normal protein values. W.B.C. 8,000. Radiography of the temporal bones and accessory sinuses showed no abnormalities. Arteriography was normal. EEG normal.

Three weeks later the condition was aggravated, with development of left-sided hemiparesis, impairment of speech and marked diplopia.

At a follow-up examination six months after the onset of the disease the patient had made a complete recovery.

Follow-up studies of the 73 patients (based on questioning of the patients and/or information from their physicians) eighteen months later showed that 5 adult patients still had some sequelæ of the disease. The predominant symptom was asthenia; but complaints of paroxysmal vertigo and depression were also voiced.

Incidentally, these studies revealed that similar, although smaller, epidemics had occurred in the same district in 1947, 1950 and 1951; of the patients attacked during these outbreaks, 5 had still paroxysmal vertigo, in 2 accompanied by asthenic symptoms.

(2) *Epidemic Dominated by Upper Respiratory Infection*

This epidemic has previously been reported (Pedersen, 1956) and will be only briefly mentioned here.

In a district with a population of about 2,000, about 50 cases of vertigo of sudden onset occurred within four months in the autumn of 1953.

XUM

Most of the cases were associated with upper respiratory infection, and slight fever was present in a few patients. The epidemic comprised 7 severe cases, which are briefly reported below.

Case 5.—A woman, aged 51, was suddenly attacked by paroxysmal vertigo; a fortnight later, slight left-sided hemiparesis and transient diplopia developed. Examination eight months later showed slight paresis of the left arm and left Babinski response; normal spinal fluid.

Case 6.—A woman, aged 32, had for a fortnight suffered from a sore throat. Sensory changes in the limbs on the right side then developed, associated with a feeling of heaviness in the right leg. The patient was very drowsy for three days, and later suffered from paroxysmal vertigo.

Case 7.—A woman, aged 34, caught a cold with slight fever; four days later muscular weakness, diplopia and impaired consciousness developed, accompanied by vertigo.

Case 8.—A boy, aged 8 years, caught a common cold. For a short period he was unable to stand on his legs. Vertigo persisted for some days afterwards.

Case 9.—A woman, aged 49, fell ill with fever of sudden onset and vertigo; she had a feeling as if tables and the bed moved up towards her. Later, diplopia, headache and difficulty in concentration developed. During subsequent attacks of vertigo she became markedly pale and nauseated, and felt very tired. Prior to the onset of the disease, the patient had been on a short tour to Norway to visit her sister-in-law, in whom fever likewise developed, accompanied by intense vertigo of a fortnight's duration. Questioning of our patient and her sister-in-law suggested that the disease had been transmitted from our patient, and that the incubation period was twelve to fourteen days.

Case 10.—A woman, aged 38, caught a cold with slight fever. This cold was followed by intense vertigo and drowsiness persisting for a fortnight.

Case 11.—A woman, aged 46, had symptoms suggestive of a common cold, with slight fever (38·5° C.) and pronounced vertigo. Afterwards drowsiness developed, associated with visual hallucinations of several days' duration and transient diplopia. This patient had visited the woman considered in Case 10 during her illness; her own disease developed about a fortnight later.

Follow-up studies four years after the disease showed that 4 of the patients still had symptoms, mainly in the form of asthenia and vertigo, while one had mild symptoms of hemiplegia. In most cases, the vertigo had persisted for from a few days to up to about twelve months; after some time it became paroxysmal and tended to be provoked by movements of the head or rapid changes in posture. The paroxysms gradually became shorter with symptom-free intervals of increasing length and ultimately entirely disappeared.

(3) *Family "Epidemic" with Vertigo and a Case of Encephalitis*

In a family consisting of the mother of 26, a boy of 5 and 3 girls of 3, 2 and 1 year, a disease manifested by vertigo, nausea and vomiting occurred within twenty-four hours on June 27 and 28, 1956.

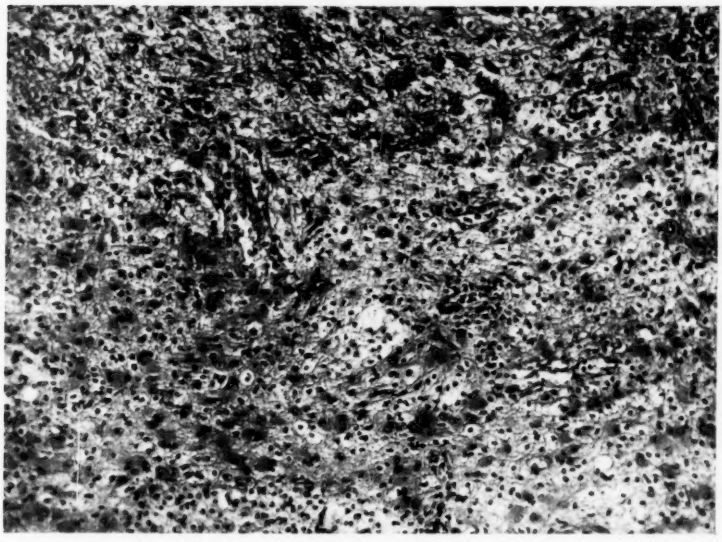

FIG. 2 (*Case 16*).—Section of cortal biopsy specimen stained with hæmatoxylin and eosin (× 285).

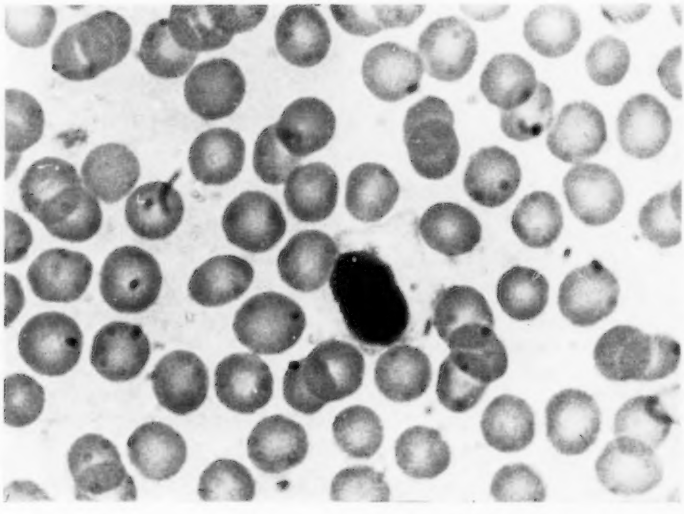

FIG. 3.—Smear showing the atypical white blood cell.

To illustrate article by Ejner Pedersen.

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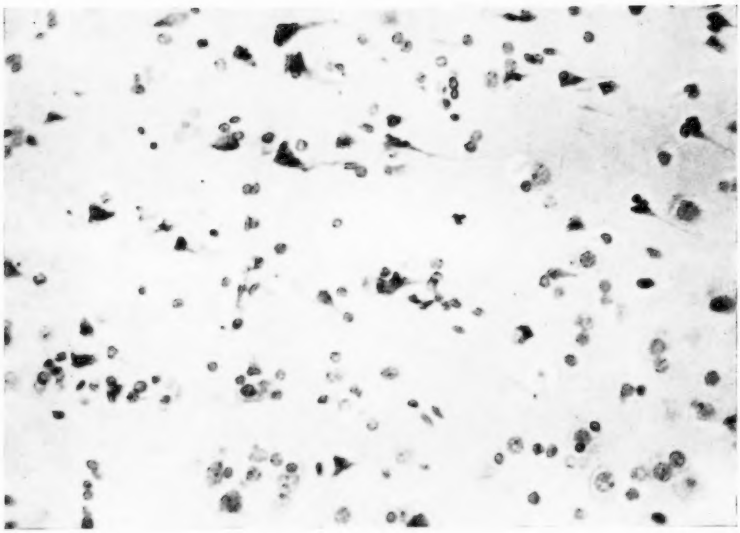

FIG. 4 (*Case 26*).—Section of cortical biopsy specimen stained with gallocyanin chromalum by the method of Einarson (× 285).

To illustrate article by Ejner Pedersen.

Case 12.—Gyratory vertigo suddenly developed in the mother, accompanied by nausea and a single episode of vomiting. She had no fever; apart from fatigue, which persisted for a few days, she felt well again after the lapse of five hours.

Case 13.—The boy, aged 5 years, suffered from vertigo for six hours, during which time he was very pale and vomited twice. During the next few days he felt very tired.

Case 14.—The girl aged 3 years also suffered from vertigo and vomited five times. During the next few days she came in often and threw herself on the floor. She was pale and very tired.

Case 15.—The girl aged 1 year vomited several times and was pale and tired for some time.

None of these patients (Cases 12–15) had any skin eruptions.

Case 16.—The girl aged 2, felt poorly on June 27; she dozed most of the time, and the next morning she was very limp. Vomiting developed and continued for the next two days. On June 29, to-and-fro movements of the eyes were noted—probably nystagmus—and the patient was unable to see anything. Later in the day, the temperature rose to 40° C. Two days later epileptic seizures with generalized tonic convulsions developed. No skin eruptions were observed.

The patient was admitted to the regional hospital; on admission, she had high fever, was limp and weak, and had frequent convulsive seizures and violent involuntary movements. Six weeks later the patient was transferred to the Department of Neurology, Aarhus, where she stayed for two and a half months. The condition was characterized by violent involuntary movements, mainly choreatic and less frequently athetosic contractions. Numerous epileptic seizures occurred, with preponderance of the limbs on the right side. Contact with the patient could not be established. Nystagmus was absent; ophthalmoscopic findings were normal. EEG was difficult to assess because of artefacts, but was apparently abnormal. Spinal fluid: 15/3 cells, slightly increased protein values. Hæmatological examination, including bleeding time, coagulation time and platelet counts, showed no abnormalities. W.B.C. 12,000, with 11 per cent atypical cells.

Ventriculography was performed six weeks after the onset of the disease. The brain tissue was soft, but great resistance was encountered in the ventricular wall. Massive, diffuse dilatation of the ventricular system, without displacement, was observed. During the ventriculography, a small fragment of occipital cortex was removed for histological examination, which showed that the structure was completely blurred, with total degeneration of the original brain tissue and cortical ganglion cells; pronounced perivascular infiltration with lymphocytes and lipid-containing macrophages was observed. Scattered areas of encephalomalacia with proliferation of vessels and gemistocytic astrocytes were present (fig. 2, Plate XLIV). Histological diagnosis: chronic encephalitis (Dr. Erna Christensen).

Follow-up examination twelve months after the onset of the disease showed that the patient was demented. The condition was still characterized by pronounced involuntary movements, mainly of an athetosic nature. Generalized spasticity and bilateral Babinski response were present. She is still alive two years after the acute disease.

In spite of energetic inquiries we did not find any other unquestionable cases outside the family; nor did the patients seem to have been in contact with similar cases in other parts of the country. There was no evidence in support of food poisoning; they had water and milk supply in common with the rest of the town. The members of the family had not had any

XUM

contacts with animals or birds; the surrounding vegetation did not contain any items of toxicological interest, apart from laburnum, which is irrelevant to the disease observed.

(4) *Epidemic Vertigo in Hospitalized Patients*

Table I shows the symptoms and signs observed in 16 hospitalized patients in whom epidemic vertigo was revealed on admission.

These 16 patients were admitted to the Department of Neurology, Aarhus, during the period 1952–1957. They were selected from among an appreciably larger number of cases on the basis of definite knowledge of the occurrence of similar cases in the patient's surroundings simultaneously with his own disease. This group represents 15 different epidemics and does not include any of the previously considered patients. Cases in which the vertigo might be referable to other causes, such as active ear disease, severe hypertension, epilepsy or intoxication, and cases with neurological signs other than nystagmus and acoustic and vestibular abnormalities were excluded. The mere fact that these patients were referred to a special neurological department undoubtedly indicates that they represent relatively severe cases.

The group consisted of 6 men and 10 women, while Wendelboe-Jørgensen (1947) had more men than women in his series. The average age of the patients was 31 years, and there were relatively few children and elderly people. This is roughly in agreement with the age distribution observed by Dix and Hallpike (1952) in patients with vestibular neuronitis, whereas several authors (Burrowes, 1952; Marshall, 1955; Alcock, 1956; Charters, 1957) found a greater average age and more elderly people among their patients with epidemic vertigo. In elderly patients, it may be very difficult to differentiate epidemic vertigo from vascular disease. Thus, the case of epidemic vertigo in a 67-year-old woman which Charters described as being typical is not absolutely convincing; this disease might just as well have been due to insufficiency of basilar circulation.

The age distribution of the hospitalized patients differs considerably from that observed in the patients affected by the aforementioned epidemic (fig. 1), but in both groups it is a striking feature that sequelæ of long duration were observed only in adults.

In 3 patients, the disease began with gastro-intestinal reactions and fever; in another 3, upper respiratory infection was the initial symptom. In 7, the vertigo was at first gyratory, while it was uncharacteristic in the remaining patients, who described it, for example, as a sensation of seasickness or a feeling as if the floor moved towards them.

During the course of the disease, the character of the vertigo often changed. At first, it occurred in episodes of long duration or was

TABLE I.—CLINICAL DATA FOR 16 HOSPITALIZED PATIENTS

Case No.	Age (yrs.)	Sex	Fever	Gastro-intest. reac-tions	Upper resp. infect.	Vertigo	Duration of symptoms on adm. (mos.)	Asthe-nia	De-pres-sion	Spinal Fluid press. (mm.)	Spinal Fluid cells	Atyp-ical W.B.C. (%)	Time of follow-up examination (mos.)	Duration of disease (mos.)
17	40	F	38·5	+	+	Other	1	+	+	120	7/3	—	36	>36
18	18	M	–	–	–	Other	1	(+)	–	200	23/3	18	12	4
19	46	M	–	–	–	Gyrat.	7	+	+	180	0/3	18	18	>18
20	48	F	–	–	–	Gyrat.	1	+	+	110	18/3	22	12	>12
21	16	F	–	–	–	Other	1	+	–	190	6/3	29	18	2
22	41	M	–	–	–	Other	60	–	–	180	2/3	9	60	>60
23	43	F	–	–	–	Gyrat.	1½	+	–	210	4/3	5	12	6
24	39	F	41·0	+	+	Other	18	+	–	190	12/3	6	36	24
25	17	F	39·8	+	+	Gyrat.	8	+	+	200	2/3	–	30	>30
26	33	F	+	–	–	Gyrat.	3	+	+	120	1/3	15	15	>15
27	11	M	39·0	–	+	Other	½	–	–	?	1/3	1	18	12
28	17	M	39·0	–	+	Gyrat.	½	+	–	100	13/3	–	24	>24
29	26	F	–	–	–	Other	½	+	+	200	2/3	6	12	>12
30	32	F	–	–	–	Other	3/4	+	–	210	12/3	7	5	2
31	24	F	+	–	+	Gyrat.	6	+	+	180	33/3	2	24	18
32	51	M	–	–	–	Gyrat.	4	+	+	110	10/3	12	18	>18

constantly present, while later on it became paroxysmal, at this stage frequently being provoked by rapid movements of the head or trunk. In most cases, the intensity of the vertigo was decreasing, but relapses just as severe or even severer than the initial attack did occur. In 5 of the 16 patients the spells of vertigo were followed by a period characterized by greatly increased fatigue and depressive and anxious reactions; this period lasted from a few hours to several days. Similar reactions were repeatedly observed in non-hospitalized patients.

The clinical picture with episodes of vertigo followed by markedly increased fatigue is strongly suggestive of the phenomena occurring in epileptic seizures. I am fully convinced that this fatigue is so pronounced that it cannot be explained merely by the patient's disappointment at having experienced another attack.

Mild tinnitus was present in 3 patients (Cases 17, 19 and 20).

All the patients were subjected to a complete otorhinolaryngological examination, in most cases supplemented by radiography of the accessory sinuses and temporal bones. Hearing tests were performed by pure-tone audiometry, in some cases also with speech audiometry, and the vestibular function was studied by the method of Fitzgerald and Hallpike. Case 19 revealed a very slight hearing impairment in the left ear without definite recruitment. Vestibular function was normal except in Case 18 (slightly reduced caloric response on one side), Case 21 (weak, equal caloric responses) and Case 32 (slightly prolonged post-rotatory nystagmus). Directional preponderance was not demonstrated. The patients were also tested for nystagmus with Bartel's biconvex glasses, in nearly all cases with the head in different positions. 3 revealed spontaneous horizontal nystagmus (only 1 patient was studied during an attack of vertigo).

The spinal-fluid findings appear from Table I. 6 showed more than 10/3 mononuclear cells. The protein content was somewhat increased in Case 22, but in the remaining at or within normal limits.

EEG was performed in all the patients, in most cases on several occasions; if the first curve was abnormal, the examination was always repeated at some later time. The EEG were normal in 12, at the border line in 2 and slightly abnormal in 2. The abnormalities consisted in slow activity without focal signs (in normal EEG, 5 to 10 per cent 6–7 c.p.s. activity without marked increase in voltage is allowed). Later, the two slightly abnormal curves both approached normal, while the others remained unchanged. Dalsgaard-Nielsen (1953) found "slight to moderate abnormality" in 6 of his 13 cases of epidemic vertigo, but his series is not comparable with the one considered here, since 5 of his 21 patients had objective neurological manifestations.

The W.B.C. counts did not reveal anything of particular interest. In 13 of the patients who were subjected to detailed hæmatological studies atypical cells were observed similar to those previously mentioned in the case

reports. This cell type (fig. 3) is reminiscent of Downey's mononucleosis cell, type II, but can nevertheless be differentiated from the latter, which, *inter alia*, has larger flakes of chromatin granules (Bichel, 1959). The cell type has been described in detail in a previous study (Pedersen, 1956). It is a striking feature that these cells were still present in many of the patients at follow-up examinations performed several years later. Blood pressure and sedimentation reactions showed nothing of interest; enlargement of the lymph nodes or skin eruptions did not occur.

Ventriculography was performed in 2 patients and showed normal conditions; in 1 of them in whom the examination was made nine months after the onset of the disease, a small fragment of tissue was removed from the occipital cortex for histological examination, which showed slight atrophy of the ganglion cells and satellitosis. In addition, round-cell infiltration into the vessel walls was observed (fig. 4). Histological diagnosis: sequelæ of encephalitis ? (Dr. Erna Christensen).

The time of the follow-up examination is also shown in the table. It should be noted that the symptoms which persisted for prolonged periods were, in particular, fatigue, depression and paroxysmal vertigo, which were often greatly incapacitating.

Finally, it must be mentioned that many patients were taken to hospital with a disease of the same nature as that observed in Cases 17–32. However, these are not included in the study because definite information as to the epidemiological background is missing, so that the delineation of the clinical picture in these patients would partially have been based on negative criteria. Incidentally, the disease may occur apparently sporadic, which we have seen on several occasions when a patient gave a history of case-to-case contact with a distant district affected by the epidemic.

As already mentioned, the clinical picture with increased fatigue following the episodes of vertigo is suggestive of epilepsy; dilantin was therefore given a trial in the treatment of patients whose disease had passed into a stationary phase. Excellent effect was obtained in a few cases, but it is, however, uncertain if this therapy is superior to previously suggested methods employing barbiturates or other sedatives.

Ætiology

Our cases of epidemic vertigo originated from outbreaks of disease often with a mixed symptomatology. However, two types seemed to be prevalent, viz. epidemics dominated by gastro-intestinal reactions, with an incubation period of one to two days, and epidemics dominated by upper respiratory infections, with an incubation period of twelve to fourteen days. The cases occurred both in urban and rural districts and did not show a predilection for any particular season of the year, which is in agreement with the observations of Charters (1957) in Kenya. In most cases, the course was short and benign, but 5 to 10 per cent of the patients

XUM

had protracted sequelæ. Our studies did not reveal any evidence which might suggest a relationship between the cases and areas of water or milk supply. The patients were not particularly people who had been in contact with domestic animals (cattle, poultry or cage birds). Our observations suggested that the disease may be spread by carriers and thus support the assumption set forth by Burrowes (1955) and Charters (1957).

We have made a large number of different investigations both in these patients and in our encephalitis patients, in particular, serological examinations of blood and spinal fluid; in acute cases, the fæces were also studied. Although not all tests were applied to each individual patient, investigations for the following diseases were performed: ECHO, coxsackie, poliomyelitis, ornithosis, St. Louis, Eastern equine, Western equine and Russian spring-summer encephalitides and lymphocytic choriomeningitis. Investigations for bacteria by cultivation and serological methods were also performed (including *Listeria monocytogenes*, *Brucella abortus*, streptococci, staphylococci; Leptospira, Q fever, Paul-Bunnell reaction; fungi). These investigations were negative, but are continued on frozen sera and spinal fluids.

Comments and Discussion

The epidemiological investigations suggest that epidemic vertigo and encephalitis may have the same ætiology, since both occurred in the same epidemic. In addition, it seems as if there are at least two different ætiologies, since two types of epidemics with incubation periods of different lengths have been observed. The disease may undoubtedly be transmitted by case-to-case contact. Otherwise the ætiology is unknown, but the observations are suggestive of an infectious disease.

A few remarks will be appropriate on the relatively intense asthenia which develops in 5 to 10 per cent of the cases and often becomes the predominant symptom in the late course. It is known that such asthenia may develop after certain neuroinfections (encephalitis, meningitis, poliomyelitis, etc.). In many of our patients, the asthenia was complicated by depression and anxiety, so that it was difficult to differentiate the condition from depressive neurosis; several of our cases were, in fact, interpreted as such at some phase of the disease. It would be of interest to know if patients with such protracted sequelæ had been neurotic before the onset of the disease. Nothing definite can be said as to this possibility; but it is my impression, which is based on conversations with the patients and their relatives and/or their physicians, that the group with prolonged asthenia and depression contained both people who had previously had neurotic symptoms and others without a history of such symptoms.

The localization of the disease has been the subject of much discussion, and nearly all possibilities have been considered. The following suggestions have been made: lesion of the Eustachian tube (Williams, 1952),

XUM

labyrinthine disease (Stewart, 1951; Mygind, 1952), infection of the ganglion of Scarpa (Charters, 1957), and, particularly, lesion of the second vestibular neurone including brain-stem affection (e.g. Wodak, 1930; Borberg, 1947; Møller, 1949, 1956; Winther, 1952; and Dalsgaard-Nielsen, 1953). Poston (1926) advanced a theory which covered nearly all the aforementioned possibilities; he assumed that the infective agent forced its way from the nasopharynx through the Eustachian tube to the middle ear and farther along the eighth cranial nerve to the vestibular nucleus.

In view of the symptomatology and the results of the otological examinations, affection of the Eustachian tube can be ruled out. A lesion of the ganglion of Scarpa is an interesting possibility; however, an isolated affection of this ganglion cannot explain that some patients suffer from tinnitus, which presupposes that the acoustic apparatus must be involved.

The main problem will therefore be labyrinthine disease versus a more centrally placed lesion. The type of vertigo and nystagmus does not give any definite information as to the localization, even though the initial vertigo, often of long duration, would by some authors be interpreted as being of central origin (*see*, e.g. Alpers, 1958). Most authors concur that "in the case of hearing loss, tinnitus is much more frequent in peripheral than in central disorders" (Alpers); hence, the rare occurrence of tinnitus and the presence of normal hearing in all but one of our patients are against the assumption of a labyrinthine affection.

The most plausible explanation seems to be a lesion of the second vestibular neurone, including the brain-stem, just as in vestibular neuronitis (Dix and Hallpike, 1952), since this disease seems to be closely related to epidemic vertigo; moreover, the results of the investigations, e.g. galvanic reflex, are suggestive of a lesion central to the ganglion of Scarpa. A similar clinical picture has also been described by Nylén (1924), Aschan and Stahle (1956) and others; it is dominated by episodes of vertigo, and upper respiratory infections are present in many cases; in one of the cases reported by Aschan and Stahle the disease began with gastro-intestinal reactions.

It is a well-known fact that lesions of the brain-stem may give rise to vertigo. Many cases of paroxysmal vertigo are on record; in some of these, neurological symptoms suggestive of brain-stem affection were observed, for example, by Gerlier (1887), Barré and Reys (1921), Wimmer (1924), Meulengracht (1947), Winther (1952), Dalsgaard-Nielsen (1953) and Charters (1957). In a series of 152 consecutive cases of encephalitis, we found that vertigo was a conspicuous symptom in 43, including 22 in whom the symptomatology was suggestive of a brain-stem lesion; this incidence is appreciably higher than that of brain-stem encephalitis observed among the total number of encephalitides. However, such figures must be taken with some reserve, partly because brain-stem encephalitis through an increase in the intracranial pressure may give

XUM

rise to distant symptoms, and partly because encephalitis must generally be assumed to be diffuse, so that it is merely a question of a certain preponderance in some region of the brain.

Against the assumption that the cause of epidemic vertigo should be sought in the brain-stem may be said that other neurological manifestations should then be expected. In this connexion it must be remembered that the present series was selected in such a manner that patients with objective neurological signs, apart from nystagmus and acoustic and vestibular findings, were excluded in order to throw light on "pure" epidemic vertigo; in some other series such neurological signs are reported. Moreover, many of the patients who were excluded from the series had symptoms bridging the gap between "pure" epidemic vertigo and massive brain-stem encephalitis, such as oculomotor paralysis, facial palsy, paræsthesiæ, facial pain, Babinski response, etc.

Both in the present series and those considered in the literature, only slight spinal-fluid changes were observed. However, 7 of 16 patients had 10/3 cells or more, and most of the patients were examined after the acute phase had passed off. The distribution of the EEG findings was roughly as might be expected in a normal series; two patients showed a slightly abnormal curve, which, however, approached normal later in the course.

Finally, it would be reasonable to consider if the lesion might be situated at a higher cerebral level. The question as to the vestibular cortical representation has not as yet been clarified, but various observations point to the temporal lobe, for example, that Spiegel (1934) by strychninization of the temporal lobe was able to induce convulsions by caloric stimulation of the ear; that Penfield and Jasper (1954) provoked vertigo by stimulation of the temporal lobe in epileptics; and that epileptic vertigo may later continue in temporal-lobe seizures (e.g. Pedersen and Jepsen, 1956). We did not reveal a history of temporal symptoms in any of our patients with epidemic vertigo; nor did we disclose focal changes in the EEG or directional preponderance in the caloric test. Thus, there were no positive signs of cortical localization, but in the case of epidemic vertigo in which cortical biopsy was performed, signs of involvement of the occipital cortex were revealed.

Spiegel and Sommer (1944) voiced the opinion that an increase in the intracranial pressure may give rise to compression of the endolymphatic sac, which through a secondary increase in the pressure in the internal ear may result in vertigo. The pressure of the spinal fluid was not strikingly high; even though this does not exclude that paroxysmal fluctuations in the pressure may occur, there were no definite indications of this.

In recapitulation, it may be said that an affection of the brain-stem seems to be the most plausible cause, but as the disease is undoubtedly infectious in nature, it cannot be excluded that the localization may vary

XUM

from patient to patient, both in the central and peripheral vestibular system.

SUMMARY

(1) Epidemic vertigo is a disease of sudden onset. The first episode is usually of relatively long duration, but later in the course of vertigo becomes paroxysmal in nature, being provoked by movements of the head or changes in posture.

(2) It is usually associated with asthenic symptoms; in the 5 to 10 per cent of the cases in which the disease is of long duration, these symptoms often become conspicuous, sometimes accompanied by depression and anxiety.

(3) The disease occurs in epidemiological association with encephalitis. Otherwise, the clinical pictures seen in the epidemics are mixed, but two main types may be made out, one which is dominated by gastro-intestinal reactions and another dominated by upper respiratory infection. Our studies suggest that the incubation periods for the two types are of different lengths.

(4) It seems as if the disease may be transmitted by carriers, but the ætiology is unknown. The disease does not show a predilection for any particular season of the year.

(5) The localization of the disease is discussed. It is found that an affection of the brain-stem is the most plausible explanation, but variation in the localization from patient to patient cannot be excluded.

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CEREBROSPINAL-FLUID PROTEINS, GLYCOPROTEINS, AND LIPOPROTEINS IN OBSTRUCTIVE LESIONS OF THE CENTRAL NERVOUS SYSTEM[1]

BY

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ALTHOUGH much attention has been given to the changes in the protein occurring in the cerebrospinal fluid of patients with multiple sclerosis (Kabat *et al.*, 1942, 1950; Yahr *et al.*, 1954; Volk *et al.*, 1955; van Sande *et al.*, 1957), neurosyphilis and other non-obstructive neurologic diseases (Hoch and Chanutin, 1952; Bauer, 1953; Cumings, 1953; Saifer *et al.*, 1956), few workers have carried out detailed investigations of the effect of obstruction in the cerebrospinal axis on the protein in the cerebrospinal fluid.

It is a well-recognized fact that the protein in the cerebrospinal fluid is increased below the level of a spinal block from any cause, and occasionally it is increased above this level, as well, though by no means so constantly. Sweet and co-workers (1954), using radioactive albumin, showed that this protein component accumulated slowly below a spinal subarachnoid block and suggested that "concentration" of the protein was occurring in this site. These workers also showed that this component collected very slowly in the obstructed ventricle. On the basis of these studies it has been suggested that the proteins are absorbed mainly from the subarachnoid space and possibly to a large degree through the arachnoid villi in the large venous channels of the cranium. Fishman and Ransohoff (1955) also demonstrated that radio-iodinated albumin appeared in greatest quantities in the lumbar sac, as compared to the ventricles. Steger (1953), using electrophoretic methods, demonstrated that prealbumin was increased in ventricular fluid, as compared to normal lumbar

[1]American Academy of Neurological Surgery Award, 1958. Presented at the twentieth annual meeting of the American Academy of Neurological Surgery, Toronto, Ontario, Canada, November 7, 1958.

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XUM

subarachnoid fluid, and that it was absent below a spinal block. This led Schaltenbrand (1953) to postulate that the source of this protein may be the choroid plexus. More recently Schmidt and Matiar (1956) have shown that the protein composition of the fluid in the lumbar space differs from that in the cisterna magna and suggest that the typical pattern of protein in the cerebrospinal fluid is due to admission of proteins above the cistern. Vymazal (1957) noted an increase of prealbumin in the region of the cistern. Thus, evidence exists that the composition of the cerebrospinal fluid is not constant throughout all the spaces that contain it.

In a previous study we presented the findings in a series of cases in which the protein in the cerebrospinal fluid was presumed to be normal in its constitution (Hill *et al.*, 1958). By the technique used we demonstrated that prealbumin, albumin, and alpha-1, alpha-2, beta and gamma globulin occur regularly in the cerebrospinal fluid. However, the relative amount of albumin in the cerebrospinal fluid in the total protein range of 35 to 50 mg. per 100 c.c. was increased as compared to those samples in which the value for total protein was 10 to 34 mg. per 100 c.c. The percentages represented by alpha-1 and gamma globulin were unchanged, and the other components were decreased. Albumin, alpha-1 globulin, and gamma globulin therefore accounted for the increase in total protein under these circumstances. From these and other findings we concluded that the increase of protein in the lumbar subarachnoid space as compared to that found in the ventricle was not due to simple concentration of the cerebrospinal-fluid protein in the lumbar space.

In the present study we shall present the data concerned with the protein composition of the cerebrospinal fluid of patients who have obstructive lesions of the cerebrospinal axis. Our results show a unique effect of obstruction on the composition of protein of the ventricular and spinal fluid. These results may contribute to the understanding of the nature of the increase of protein in the cerebrospinal fluid both in normal and in abnormal conditions.

We have added to these studies the estimation of the total glycoprotein of the cerebrospinal fluid, as well as the electrophoretic fractionation of the glycoprotein components. The total glycoprotein in the cerebrospinal fluid as we determine it refers to all protein-bound hexoses but not to protein-bound hexosamine. We are determining only the hexose portion of the protein-bound hexose. The determination should not be confused with the determination of seromucoid or mucoprotein. The latter substance is a glycoprotein containing hexose, hexosamine and protein, and it migrates with the alpha-1 globulin on electrophoretic separation. When an electrophoretic analysis using periodic acid-Schiff stain is performed, the hexose and hexosamine portion of this component are stained in the position of alpha-1 globulin. An increase of alpha-1 globulin glycoprotein therefore, by our method, may reflect an increase in

seromucoid. We have previously determined the normal range of the glycoprotein in cerebrospinal fluid and have demonstrated that when the protein concentration is normal, most of the glycoprotein usually occurs in albumin and beta globulin fractions. The amount of alpha-1 globulin glycoprotein was variable but usually less than the amounts of the other components, except gamma globulin glycoprotein which was absent or barely demonstrable. Also, Baudouin and co-workers (1954) and Bauer (1957) have demonstrated that the greater part of the glycoprotein in cerebrospinal fluid is found normally in the beta globulin position. In serum the main concentration is in the alpha-2 globulin position (Hill *et al.*, 1958). The results of the present study show that in certain obstructive states the glycoprotein in the cerebrospinal fluid increases; the increase is mainly that of alpha-1 globulin glycoprotein.

The demonstration of lipoproteins in cerebrospinal fluid has been difficult. We have demonstrated the beta globulin lipoprotein in only two cases in the present series. However, in certain non-obstructive neurologic diseases beta globulin lipoprotein or an equivalent substance can be demonstrated.

Material

Ventricular fluid with a protein content of less than 35 mg. per 100 c.c. was obtained from 7 patients with no obstruction in the ventricular system and from 14 patients with ventricular obstruction at some point between the foramen of Munro and the distal portion of the fourth ventricle. The obstruction in most cases appeared to be complete or nearly complete. In 3 of the latter cases of ventricular obstruction fluid was obtained also from the lumbar subarachnoid space. In an additional 5 cases ventricular fluid was obtained from patients with infantile communicating hydrocephalus of unknown ætiology; in 1 of these cases the ventricular protein measured 120 mg. per 100 c.c. In addition the ventricular fluid of a patient with papillœdema who had a tumour of the spinal cord was examined.

In 6 other cases spinal fluid was obtained from below a partial block caused by a tumour or protruded disc in the cervical region. In an additional 6 cases fluid was obtained from below a complete block of the cervical or thoracic subarachnoid space.

The fluid from a subdural hygroma in 2 cases and from a subdural hæmatoma in 1 case was examined.

Method

An aliquot of fluid was examined for cells, total protein, total glycoprotein and Kolmer reaction for syphilis. The remainder was centrifuged and concentrated by ultrafiltration in collodion sacs. Paper electrophoresis was performed and parallel strips were stained for proteins, glycoproteins and lipoproteins. The results were calculated on a Spinco analytrol. The method is described in detail elsewhere (Hill *et al.*, 1958).

Results

Protein.—The results of protein examination in a group of persons who had no ventricular obstruction are given in Table I. Normal values for ventricular, cisternal and lumbar subarachnoid fluid protein are listed in this table.

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TABLE I.—COMPOSITION OF CEREBROSPINAL FLUID AT VARIOUS SITES IN THE CEREBROSPINAL AXIS OF SUBJECTS WITH NO NEUROLOGIC DISEASE

Site	*Total protein, mg./100 c.c. (mean)*	*Prealbumin, per cent*	*Albumin, per cent*	*Globulin, per cent*			
				Alpha-1	*Alpha*-2	*Beta*	*Gamma*
Ventricle (7)*	17·1 ± 9·9†	6·3 ± 1·8	46·4 ± 6·5	8·1 ± 1·7	7·9 ± 2·8	19·1 ± 2·0	10·3 ± 2·7
Cistern (13)	18·3 ± 4·3	4·6 ± 1·6‡	44·6 ± 7·3	6·7 ± 1·0	9·5 ± 3·7	21·3 ± 4·5	13·4 ± 4·0§
Lumbar region‖							
Normal persons							
Group A (10)	21·0 ± 7·3	5·5 ± 1·1	45·0 ± 6·0	6·8 ± 2·6	9·6 ± 2·3	21·6 ± 4·7	11·1 ± 2·7
Group B (11)	39·5 ± 4·8	3·9 ± 0·8¶	54·0 ± 3·5**	6·5 ± 2·1	7·3 ± 1·6¶	15·9 ± 3·6¶	11·4 ± 2·2
Group C (6)	59·1 ± 3·8	3·3 ± 1·1¶	55·6 ± 2·6**	5·6 ± 2·3	8·4 ± 0·4	16·5 ± 3·8	10·5 ± 3·0
Persons undergoing pneumoencephalographic examination							
Group D (12)	21·0 ± 6·5	5·4 ± 1·7	46·4 ± 3·6	6·3 ± 2·4	10·5 ± 2·6	18·8 ± 3·7	12·6 ± 3·7
Group E (13)	42·3 ± 4·8	3·5 ± 1·2¶	53·6 ± 5·6**	5·9 ± 1·6	8·6 ± 1·2	17·6 ± 1·2	10·0 ± 2·5

*Number of cases given in parentheses.
†The value following ± indicates one standard deviation.
‡Significantly lower than in ventricular fluid.
§Significantly higher than in ventricular fluid.
‖Range of values for total protein in mg./100 c.c.: group A, 10–34; group B, 35–50; group C, 50 and over; group D, 10–34; group E, 35–50 mg.
¶Significantly lower than in group A.
**Significantly higher than in group A.

TABLE II.—EFFECT OF INTRAVENTRICULAR OBSTRUCTION ON PROTEIN COMPOSITION OF CEREBROSPINAL FLUID

Source of fluid	*Total protein, mg./100 c.c.*	*Prealbumin, per cent*	*Albumin, per cent*	*Globulin, per cent*			
				Alpha-1	*Alpha*-2	*Beta*	*Gamma*
Ventricle (15)*	13·0 ± 7·5†‡	14·0 ± 5·0	36·6 ± 10·8	7·6 ± 2·8	9·0 ± 2·7	20·7 ± 5·9	11·3 ± 3·6
Lumbar space (3)	127·0 ± 41·0	1·8 ± 0·4	56·9 ± 1·4	7·0 ± 2·4	8·8 ± 1·8	14·2 ± 1·8	11·0 ± 1·2

*Number of cases given in parentheses.
†Three values for total proteins reported as less than 10 mg./100 c.c.
‡The value following ± is the standard deviation.

TABLE III.—EFFECT OF SPINAL SUBARACHNOID OBSTRUCTION ON THE PROTEIN CONTENT OF LUMBAR SPINAL FLUID

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Condition	Total protein, mg./100 c.c.	Prealbumin, per cent	Albumin, per cent	Globulin, per cent			
				Alpha-1	Alpha-2	Beta	Gamma
Normal (21)*	31·3± 9·5†	4·6±1·3	49·5±6·5	6·7±2·0	8·3±2·1	18·5±4·8	11·2±2·7
Spinal obstruction							
Partial (6)	55·0± 5·4‡	2·8±0·7§	56·8±4·3‡	7·0±0·6	7·0±1·9	16·0±1·7	10·0±2·0
Complete (6)	416·5±241·0‡	1·0±1·2§	53·5±5·4‡	8·3±1·5‡	7·4±1·7	15·6±3·2	14·1±3·9‡

*Number of cases given in parentheses.
†The value following ± is the standard deviation.
‡Significantly higher than those of normal controls.
§Significantly lower than those of normal controls.

TABLE IV.—PROTEIN CONTENT OF CEREBROSPINAL FLUID FROM VENTRICLE IN COMMUNICATING HYDROCEPHALUS

Case	Total protein, mg./100 c.c.	Prealbumin, per cent	Albumin, per cent	Globulin, per cent			
				Alpha-1	Alpha-2	Beta	Gamma
1	10	9·0	33·0	6·0	12·0	30·6	9·0
2	20	6·2	35·7	5·4	14·3	28·6	9·6
3	40	7·6	41·4	5·4	10·8	20·6	14·2
4	40	3·8	50·0	5·7	9·5	23·4	7·6
5 Left	120	3·0	57·0	6·0	8·0	18·0	8·0
Right	120	3·0	58·0	5·0	8·0	18·0	8·0

TABLE V.—COMPOSITION OF FLUID OF SUBDURAL HYGROMA AND SUBDURAL HÆMATOMA

Condition	Total protein, mg./100 c.c.	Prealbumin, per cent	Albumin, per cent	Globulin, per cent			
				Alpha-1	Alpha-2	Beta	Gamma
Subdural hæmatoma	550	—	46·2	10·7	9·8	15·6	17·2
Subdural hygroma							
Case A	500	1·4	49·3	11·4	7·2	20·7	10·0
Case B							
Sample 1	1,000	1·0	64·0	8·0	8·0	12·0	9·0
Sample 2	30	10·0	34·0	18·0		24·0	14·0

TABLE VI.—NATURE OF CEREBROSPINAL-FLUID GLYCOPROTEIN IN OBSTRUCTIVE NEUROLOGIC DISEASE

Condition	Total glycoprotein, mg./100 c.c.	Albumin, per cent	Globulin, per cent			
			Alpha-1	Alpha-2	Beta	Gamma
Normal (7)*	1·1±0·5†	25·0±9·7	21·5±4·4	18·8± 9·9	33·5±6·2	Trace
Spinal obstruction						
Partial (4)	1·1±0·2	22·2±5·3	25·0±2·7	16·2± 2·2	22·0±1·2	10·2±7·5
Complete (6)	9·8±8·5	13·8±5·0	38·3±5·7	19·1±10·0	19·5±7·8	6·3±3·7

*Number of cases given in parentheses.
†The value following ± is the standard deviation.

Table II gives the findings in intraventricular obstruction. The total protein of ventricular fluid is less in the presence of intraventricular obstruction than in the absence of such obstruction. Actually, the mean value for fluid from cases of obstruction may even be somewhat lower than that presented in Table II. Three samples of this group were reported as having a protein content of less than 10 mg. per 100 c.c. by the sulphosalicylic method. This method is not exact but is the one generally used in most hospitals.

In the ventricular fluid from cases of intraventricular obstruction the prealbumin component was markedly increased, the albumin was decreased and the beta globulin was slightly increased. The specimens of lumbar fluid in 3 of these cases showed a diminution in the percentage of prealbumin and an increase in the percentage of albumin. The lumbar fluid was markedly different from that obtained from above the block in the ventricles and had a higher concentration of protein (fig. 1).

Table III shows the effects of partial obstruction of the cervical subarachnoid space upon the lumbar fluid. When the fluid of patients with obstruction is compared with the fluid of normal persons who have a low concentration of protein in the cerebrospinal fluid a significant difference is noted—prealbumin is decreased and albumin is increased. In complete obstruction, as seen in Table III, the total protein content was high and the prealbumin fraction was absent in 2 cases and markedly diminished in the remainder; the concentration of alpha-1 globulin was increased in 4 of the 6 cases. The proportion of gamma globulin was increased, but only as the total protein increased. The electrophoretic pattern from a typical case is presented in fig. 2B.

In Table IV the data obtained from examination of ventricular fluid in 5 cases of communicating hydrocephalus are presented. In 3 cases the concentration of protein was greater than normal[1]; mainly the albumin component was increased. In 2 cases in which the total protein content was normal there was a normal pattern for protein in ventricular fluid.

The results of analysis of fluid from 1 subdural hæmatoma and 2 subdural hygromas are given in Table V. Fluid from the subdural hæmatoma did not contain prealbumin and, except for the presence of increased amounts of alpha-1 globulin, it resembled serum in composition. Its composition most closely resembles that of the fluid collected from cerebral cysts associated with tumours. Fluid from the 2 cases of subdural hygroma contained prealbumin, and more beta globulin than gamma globulin. In this respect the hygroma fluid resembles cerebrospinal fluid. However, it contained increased amounts of alpha-1 globulin. In 1 case a second sample, collected four days after the first, had the characteristics of ventricular fluid.

[1]A concentration of 30 mg. per 100 c.c. was considered as the upper limit of normal for ventricular fluid.

XUM

PLATE XLVI

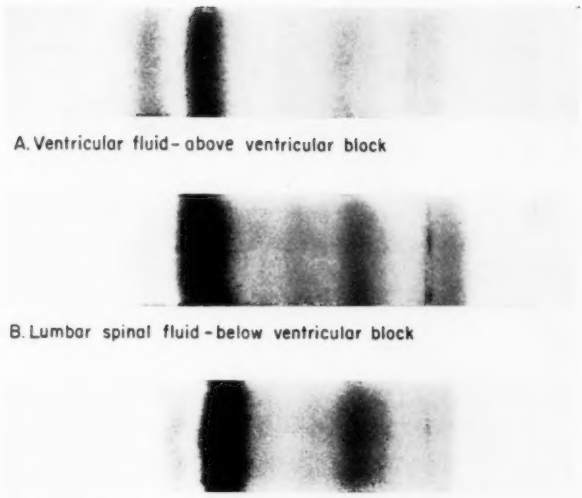

FIG. 1.—Normal proteins in cerebrospinal fluid (strip C) are a mixture of proteins derived from the region of the ventricles (strip A) and the subarachnoid space (strip B).

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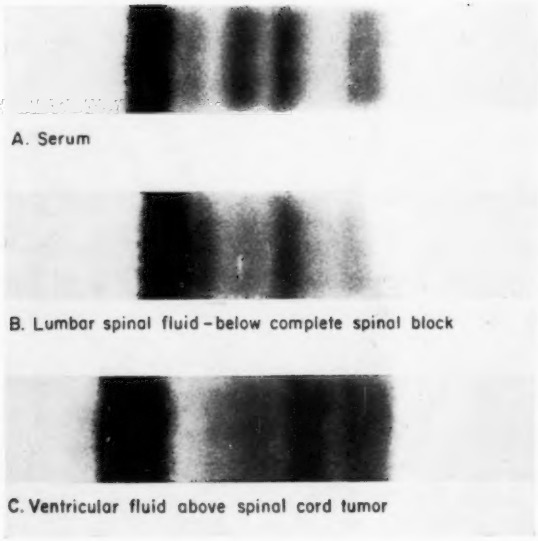

FIG. 2.—The serum (strip A) of this patient with metastatic carcinoma contains an increased amount of alpha-2 globulin. The cerebrospinal fluid (strip B) of the same patient obtained from below a spinal block does not resemble serum or normal cerebrospinal fluid (strip C, fig. 1). It contains no prealbumin but contains increased amounts of alpha-1 globulin. The electrophoretic pattern of the ventricular fluid of a patient with a tumour of the spinal cord is shown in strip C. This probably represents the admission of varying amounts of serum components (for example, as the result of a change in permeability of the barrier between the blood and the cerebrospinal fluid). Alpha-1 globulin is virtually absent.

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PLATE XLVIII

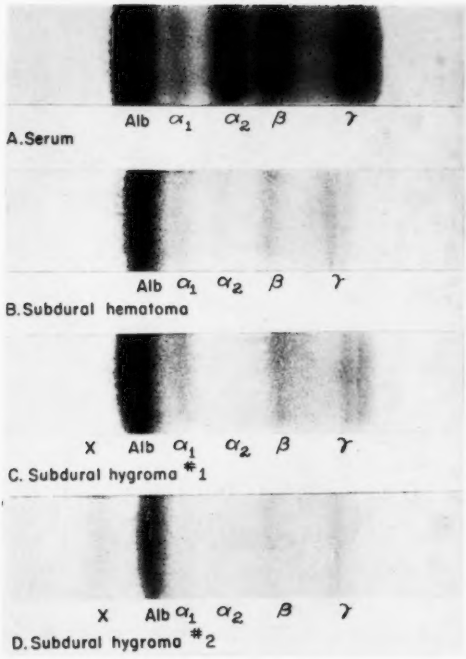
Alb α_1 α_2 β γ
A. Serum
Alb α_1 α_2 β γ
B. Subdural hematoma
X Alb α_1 α_2 β γ
C. Subdural hygroma #1
X Alb α_1 α_2 β γ
D. Subdural hygroma #2

FIG. 3—Fluid from a subdural hematoma (strip B) does not contain prealbumin, and so does not resemble cerebrospinal fluid; neither is it a perfect replica of serum (strip A). It resembles the fluid found in cerebral cysts. Fluid from a subdural hygroma (strip C) does contain prealbumin (X) though it is faintly seen. The fluid represented in strip D was obtained from a reaccumulation of fluid in the same patient four days later, and prealbumin (X) is faintly represented.

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XUM

PLATE XLIX

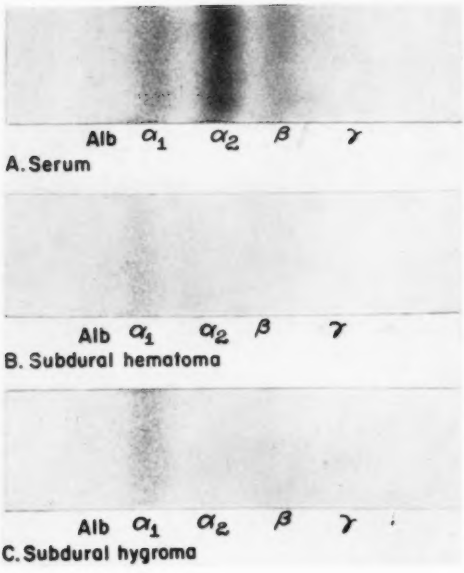

FIG. 4.—Most of the glycoprotein is in the alpha-1 position in fluid from subdural hygroma, in contrast to serum, where it is in the alpha-2 position.

To illustrate article by Norman C. Hill, Norman P. Goldstein, Bernard F. McKenzie, Warren F. McGuckin and Hendrik J. Svien.

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PLATE L

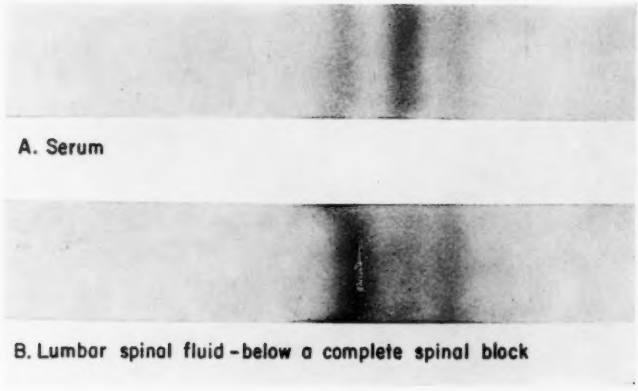

FIG. 5.—The main concentration of glycoprotein in fluid obtained from below a spinal block is in alpha-1 position and may represent seromucoid (strip B). The glycoprotein pattern, like that of the protein (fig. 2), is not a replica of that of the serum.

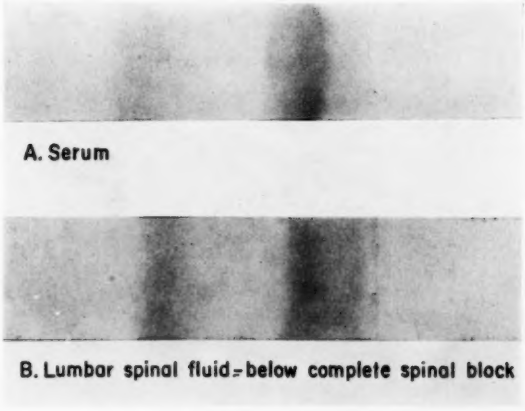

FIG. 6.—The lipoprotein in spinal fluid from below a complete block (strip B) resembles that found in serum (strip A), but there is more alpha-1 lipoprotein in relation to beta lipoprotein in the fluid from below the block.

To illustrate article by Norman C. Hill, Norman P. Goldstein, Bernard F. McKenzie, Warren F. McGuckin and Hendrik J. Svien.

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The electrophoretic pattern of a sample of fluid from a subdural hæmatoma, collected at the fourth subdural aspiration in a child, is illustrated in fig. 3B. No prealbumin is present. There appears to be an increased amount of alpha-1 globulin. Prealbumin, designated "X," is faintly present in strip C but the difference between the proteins of the subdural hygroma and those of the subdural hæmatoma in strip D is obvious. The only glycoprotein present in significant amounts in either instance is alpha-1 globulin glycoprotein (fig. 4).

Glycoproteins.—The distribution of polysaccharides in the cerebrospinal fluid of normal persons and in that of patients with partial or complete spinal subarachnoid obstruction is shown in Table VI. This table and fig. 5 illustrate the increase of alpha-1 globulin glycoprotein that occurs in a case of spinal obstruction. The increase in alpha-1 globulin glycoprotein in the cerebrospinal fluid represented in fig. 5 should be contrasted with the marked increase in the alpha-2 globulin glycoprotein in the serum of the same case. In addition, as shown in Table VI, as the total protein content of the cerebrospinal fluid increases the gamma globulin glycoprotein becomes evident.

Table VII gives the findings in respect to the total protein and glycoprotein components of the cerebrospinal fluid of patients with various obstructive neurologic conditions.

TABLE VII.—CEREBROSPINAL-FLUID PROTEIN AND GLYCOPROTEIN IN OBSTRUCTIVE NEUROLOGIC DISEASE

Site of obstruction	*Protein, mg./100 c.c.*	*Glycoprotein, mg./100 c.c.*
Ventricle		
No obstruction (7)*	17·1 ± 9·9†	0·9 ± 0·5
Intraventricular obstruction (15)	13·0 ± 7·5	0·7 ± 0·9
Lumbar subarachnoid space		
Normal		
Group A‡ (10)	21·0 ± 7·3	0·9 ± 0·4
Group B (11)	39·5 ± 4·8	1·1 ± 0·4
Partial spinal obstruction (6)	55·0 ± 5·4	1·1 ± 0·2
Complete spinal obstruction (6)	416·5 ± 241·0	9·8 ± 8·5
Ventricular obstruction (3)	127 ± 41·0	1·9 ± 0·9

*Number of cases given in parentheses.
†The value following ± is the standard deviation.
‡Range of normal values for total protein in mg./100 c.c.: group A, 10–34; group B, 35–50.

Lipoproteins.—Lipoproteins could be demonstrated in the cerebrospinal fluid below the level of complete spinal obstruction in 2 cases. They appear to be in the same position as the corresponding components of serum (fig. 6).

COMMENT

Obstructive lesions in the ventricular system.—It is well recognized that the total protein of the ventricular fluid is usually less than that of the fluid

in the lumbar subarachnoid space. The usual explanation is that the protein in the lumbar subarachnoid fluid is merely more concentrated. If this were so, the actual electrophoretic analysis of the protein in the lumbar subarachnoid fluid should be the same as that in the ventricles. In normal persons, however, we have noted that there are definite though slight differences in composition of the protein of the ventricles as compared with that in the lumbar space (Table I). One hesitates to attribute too much significance to these slight differences under normal conditions because of the recognized margin of error present in electrophoretic techniques. However, when there is a block in the ventricular system, the differences in concentration between the protein of the ventricles and that of the lumbar space are so much accentuated in the direction of their normal variations that they cannot be ignored (Table II).

The main differences then apparent are (1) that the total protein of the fluid in the ventricles is much less than that in the lumbar space and (2) that the ventricular protein contains a relatively greater amount of the prealbumin component, which is markedly increased in the presence of intraventricular obstruction.

One explanation of these findings might be that the cerebrospinal-fluid proteins are normally absorbed in the ventricles and that this pathway is occluded by the ventricular obstruction. Absorption of protein in the ventricles is unlikely in view of the results of radioactive tracer studies (Sweet *et al.*, 1954). It also seems unlikely that a substance of small molecular weight, such as prealbumin, would fail to be absorbed in the ventricles when substances of higher molecular weight, such as the globulins, are absorbed almost completely. For these reasons, failure of absorption of the protein in the ventricles seems to be an unlikely explanation.

Similarly, a change in the barrier between cerebrospinal fluid and blood in the lumbar space, because of ventricular obstruction, does not seem reasonable.

Sweet and co-workers (1954) have postulated that cerebrospinal-fluid protein is absorbed somewhere over the surface of the cerebral cortex. An explanation for the increased protein in the lumbar space below a ventricular block may be that the secondary pressure effects of the block at the foramen magnum and at the tentorium cause obstruction in this pathway of absorption. The difference in composition of the proteins in the ventricular and lumbar space is explainable, we believe, on the basis that under normal circumstances the environs of the ventricles are the usual source of prealbumin, whereas the subarachnoid space below the foramen contributes most of the remaining components of the protein in the cerebrospinal fluid. A block between these two areas results in an accumulation of the protein components characteristic of the fluid of the

XUM

non-obstructed space (that is, prealbumin in the ventricles and albumin in the subarachnoid space).

To recapitulate, therefore, the results of our studies in ventricular obstruction, and the findings of other investigators, lead us to believe that under normal circumstances the environs of the ventricles contribute the prealbumin protein, whereas the remainder of the cerebrospinal-fluid protein originates mainly in the subarachnoid space. The two normally mix and are probably absorbed somewhere above the foramen magnum.

Obstructive lesions in the subarachnoid space.—Another well-recognized fact is that the concentration of total protein in the lumbar space may vary between 10 and 50 mg. per 100 c.c. in normal subjects. The explanation generally given is that the fluid is simply more concentrated when the higher concentration of protein prevails. If this were so, the composition of the protein at 10 mg. per 100 c.c. should be the same as at 50 mg. per 100 c.c. Our results in normal subjects suggest that this is not the case, but that slight though consistent differences are present (Table I). These differences suggest that the increase is due to the addition of albumin (molecular weight 69,000) and, to a lesser extent, alpha-1 globulin (molecular weight 45,000) and gamma globulin (molecular weight 156,000 to 1,000,000), and imply that perhaps these substances of lower molecular weight tend to accumulate in the lumbar space more readily than do those of higher molecular weight such as beta globulin (molecular weight 90,000 to 1,300,000) and alpha-2 globulin (molecular weight 300,000 to 1,000,000). Again one hesitates to place too much significance on minor differences in the results of electrophoretic analyses of fluids with low concentration of protein.

However, when a complete spinal block occurs, most of the increase in total protein is due to the addition of albumin, with a relative increase in the amount of alpha-1 globulin and to a lesser extent gamma globulin (Table III).

It is difficult to envision a dynamic process from the results of examination of a single specimen. It seems logical to presume, however, that below a spinal block the protein of small molecular weight gets in first and increases until its gradient with blood is reduced to the point where no further passage takes place. Each protein would thus equilibrate at a different rate, probably determined by physicochemical properties, such as molecular weight. The amount and composition of the protein in the lumbar space below a complete spinal block would therefore be dependent on the length of time the block had been present, and the fluid would in its final stages resemble serum. Such a finding is in accordance with our results; in one of our patients with a very high concentration of protein (fig. 6), the fluid was very similar to serum, even to the presence of beta lipoprotein.

XUM

We would point out that the explanation given above does not necessarily imply any change in the barrier between the blood and the cerebrospinal fluid, but does presume that normally an absorption of protein takes place at some level above the lumbar space. In some cases a change in permeability of the blood-cerebrospinal fluid barrier may occur. This probably explains those cases in which the protein is increased above the block. It should be noted that in the case we had for study the protein pattern was much different from that usually seen below a complete block.

Finally, the possibility that the lesion itself contributes some of the protein to the fluid below the block cannot be ignored. Alpha-1 globulin contains much glycoprotein, and may represent seromucoid, a substance sometimes found near degenerating lesions (Catchpole, 1950). Recent evidence indicates, however, that the actual source of this protein may be the liver (Miller, 1957).

To recapitulate, our results along with the results of other investigators suggest that under normal circumstances the proteins that accumulate in the lumbar subarachnoid space probably do so on the basis of high gradient of concentration between the protein of the serum and that of the cerebrospinal fluid in the lumbar space; the serum proteins of low molecular weight tend to cross most easily. The protein concentration of the lumbar cerebrospinal fluid remains low when these proteins have free access to structures at higher levels in the cerebrospinal axis. When this access is obstructed, each protein in the obstructed space increases at a different rate, and the mixture, after a period of time, approaches the protein composition of serum.

Communicating hydrocephalus.—Recent work has indicated that the arachnoid villi, which formerly were thought to be the main pathway for absorption of cerebrospinal fluid, may actually be a pathway of absorption of protein. The pathologic feature that characterizes communicating hydrocephalus is an inability to resorb the cerebrospinal fluid if the block occurs outside the ventricular system. One cannot, of course, equate absorption of cerebrospinal fluid with that of protein, without experimental proof. But if the absorption of cerebrospinal fluid does depend on the absorption of its protein, or certain of its protein components, one would expect in cases of communicating hydrocephalus that the total protein or one of the component proteins in cerebrospinal fluid would increase.

We have reviewed the concentrations of total protein at ventricular levels in 12 cases of communicating hydrocephalus. In all cases dye was obtained from the lumbar subarachnoid space after intraventricular placement. The mean ventricular concentration of protein in these cases was 31 mg. per 100 c.c. In 6 of the 12 cases, however, it was less than 30 mg.

XUM

An increase in total protein therefore is not necessarily a concomitant feature of communicating hydrocephalus.

In an attempt to discover if a specific protein component increased in this condition the ventricular fluids in 5 cases (Table IV) mentioned under "Material" were studied by electrophoretic techniques. In 3 of these, protein in the ventricular fluid was increased and it was obvious that an increase of albumin accounted for most of the increase of total protein. In the 2 cases in which the concentration of protein was normal the fluid resembled normal ventricular fluid except for a slight increase of beta globulin. It is evident, therefore, that no one protein component is invariably associated with the failure to absorb cerebrospinal fluid.

It seems obvious that although an increase of protein can be associated with a defect in the absorption of cerebrospinal fluid, one cannot equate the failure to absorb spinal fluid with the failure to absorb all or any specific protein substance. This observation would seem to rule against the likelihood that the site or process of absorption of fluid and the site or process of absorption of protein are one and the same, though the absorption of both may, of course, be effected occasionally by the same pathologic process.

Chronic subdural hygroma and hæmatoma.—Occasionally, clear fluid collects between the arachnoid and dura over the cerebral hemispheres. Usually the collection follows injury and is thought to be due to a tear in the arachnoid, although its origin has never been clearly determined.

The evidence from our study indicates that the composition of the fluid of subdural hygroma more closely resembles that of cerebrospinal fluid than that of serum (Table V). We believe that the increase of protein in subdural hygroma is due to concentration of the normal protein components of cerebrospinal fluid, which in turn is due to a defect in the normal pathways of absorption of protein.

While the fluid of subdural hæmatoma is not exactly similar to serum, the proteins of this fluid have a composition characteristic of serum (Table V). The composition is also much like that of fluid found in cysts associated with cerebral tumours. We believe that the protein in the fluid of subdural hæmatoma is probably derived locally from the serum, and owes its composition to the interplay of physicochemical factors, such as the size of the serum protein molecules and their gradient of concentration across a separating membrane.

Glycoproteins.—Several investigators (Roboz *et al.*, 1955, 1957; Stary *et al.*, 1956; Apostol *et al.*, 1956) have recently indicated that estimation of glycoprotein may be of value in neurologic diagnosis. From Table VII it is seen that in cerebrospinal fluid in which the concentration of total protein was in the approximate range of 17 to 50 mg. per 100 c.c. the concentration of total glycoprotein was normal We believe that this

XUM

circumstance arises because the increase of protein in the cerebrospinal fluid is due mainly to albumin, which (in the serum, at least) contains only small amounts of glycoprotein. At higher concentrations of total protein in the cerebrospinal fluid, globulins tend to be added (such as the addition that occurs below a complete spinal block) and the glycoprotein increases disproportionately because globulins contain increased amounts of glycoprotein.

Summary and Conclusions

Normally the proteins in cerebrospinal fluid consist of a mixture of two distinct groups of proteins. One group tends to accumulate in the ventricles, the other in the subarachnoid space. The proteins that accumulate primarily in the subarachnoid space usually contribute in a greater degree to the pattern of total protein in the cerebrospinal fluid. The proteins that accumulate in the lumbar subarachnoid space seem to do so on the basis of physicochemical properties such as increasing molecular weight and a gradient between their concentration in serum and their concentration in cerebrospinal fluid. The proteins, particularly prealbumin, that characterize ventricular fluid, however, probably are present as the result of some active process in the tissue of the central nervous system. Our results support the theory that this mixture of proteins is absorbed somewhere above the foramen magnum, outside the ventricular system.

Various blocks to the flow of cerebrospinal fluid that occur in the cerebrospinal axis produce changes in the protein components of that fluid. There is usually an increase in the protein component normally characteristic of the fluid of the non-obstructed space. However, in the case of spinal obstruction, these protein patterns differ in accordance with the length of time the block has been present and may occasionally be modified by changes in the barrier between the blood and the cerebrospinal fluid, and possibly by the addition of products (particularly seromucoid) from the lesion itself.

The failure of resorption of fluid from the cerebrospinal fluid in communicating hydrocephalus cannot be equated with the failure of resorption of proteins or with the overproduction or retention of a specific cerebrospinal-fluid protein.

The proteins in the fluid of subdural hygroma contain a component characteristic of cerebrospinal fluid (prealbumin), whereas those from subdural hæmatoma do not. This suggests that the proteins in the fluid of subdural hygroma are derived from those in cerebrospinal fluid and may be associated with a defect in resorption of cerebrospinal fluid. The proteins in the fluid of subdural hæmatoma are similar to those of serum and are probably derived locally from the serum.

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XUM

THE CELLULAR CONTENT OF THE ENDONEURIUM OF PERIPHERAL NERVE

BY

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THE structure of the perineurium or laminated sheath of a peripheral nerve is distinctive and has been clearly recognised, but the packing material between nerve fibres within a single perineural sheath has always given rise to considerable difficulty among neuro-histologists. The importance of this tissue is not only concerned with the regeneration of peripheral nerves but also with the possible origins of tumours of peripheral nerve.

One of the clearest and most commonly quoted descriptions of the sheath of nerves is that of Nageotte (1932), and it is interesting to note that whilst he is quite clear on the limits of the epi- and perineurium and of the nerve fibre with its Schwann or neurilemmal sheath, the intermediate tissue is not very fully described. He concludes that the endoneurium is a connective tissue structure with a collagenous framework moulded round the nerve fibre, and "all of these collagenous formations which constitute the endoneurium are associated with fibroblasts." Cajal (1933) illustrates interstitial connective tissue cells between the fibres inside the perineurium, but le Gros Clark (1958) is more cautious for, whilst recognizing the fibrous stroma of the endoneurium and admitting that "each fibre is thus enclosed in its own endoneurial tube of connective tissue," he does not go on to describe the cells from which this fibrous tissue originates.

If again one considers the approach by the pathologist, the endoneurial cell is accepted as an entity, and the discussion is concerned with whether its origins are from neurectoderm (Masson, 1932; Murray, Stout and Bradley, 1940) on the one hand, or from mesoderm (Mallory, 1914; Penfield, 1932; Bailey and Herrmann, 1938; Tarlov, 1940). The actual number of endoneurial fibroblasts has been considered in relationship to Wallerian degeneration (Abercrombie and Johnson, 1946; Joseph, 1947; Thomas, 1948) and it is clear that whilst it is possible to assess the total cellular content within a given transverse section of a peripheral nerve by

counting the nuclei after staining, considerable difficulty arises in trying to differentiate between Schwann nuclei and the nuclei of endoneurial fibroblasts. Joseph (1947), examining the changes in nuclear population in the anterior mesenteric nerve of the rabbit during degeneration, makes no attempt to define the type of cell to which the nuclei belong. But Thomas (1948), examining similar problems in the degeneration of peripheral motor and sensory nerves, admits to considerable difficulty in differentiating the endoneurial and tubal nuclei in the sural nerve, and uses as a base-line the differential nuclear count after five days' degeneration, concluding that the tubal nuclei of both the NGM and sural nerves amount to roughly 50 per cent of all the nuclei, the endoneurial about 40 per cent and the endothelial nuclei of the blood vessel walls 10 per cent.

In examining many sections of peripheral nerve under the electron microscope over the last few years, it has been increasingly apparent to us that fibroblasts within the perineurium are very rare, and with the increasing facility of thin sectioning, it has now been possible to obtain complete transverse sections of peripheral nerves and from these to arrive at a quantitative estimate of the cellular content within the perineurium by electron microscopic examination.

Observations

Transverse sections have been examined of the sural nerve of the mouse, rat and rabbit, peroneal nerve of the rat and the nerve to the medial head of gastrocnemius of the rabbit. The material was fixed for half an hour in Palade's buffered osmium tetroxide at 4° C. and thereafter embedded in methacrylate and cut on a Cook and Perkins ultra-microtome in suitable thin sections. It was possible to examine the cytoplasmic relationship of all the nuclei in a given transverse section except for those obscured by the bars of the copper grid; however, by examining a series of random sections from each nerve it is unlikely that any bias has been introduced into the counts by the omission of the nuclei thus obscured. In a unifascicular nerve trunk or a single fasciculus of a composite nerve the perineural boundary is very clearly distinguishable in low power electron micrographs consisting of circumferentially orientated cells such as are shown in fig. 1, Plate LI. An elongated nucleus is seen running across the pictuer with the perineural lamellæ, and outside this the transversely cut dense bundles of collagen; within the perineurium are two myelinated fibres again closely packed by transversely cut collagen bundles.

All the nuclei within the perineurium were examined first at low power and then at higher resolution on the screen of the electron microscope, and in this way it was possible to distinguish between Schwann nuclei, endothelial nuclei and other nuclei; many typical examples were photographed, and doubtful nuclei were also photographed for further examination. Fig. 2 shows a nucleus associated with a typical myelinated fibre; the

small size of the myelinated fibre may be due to local compression by the large nucleus, but the typical relationship is seen with the inner and outer mesaxons at A and B and the concentric lamellæ of osmophilic material, numbering 10 in all. These nuclei are closely comparable to the tubal nuclei described in optical histology. The most interesting group of nuclei is illustrated by fig. 3, which shows a Schwann cell nucleus with 14 small non-myelinated fibres enfolded in varying degrees within its cytoplasm. These fibres vary between 1/4–1μ in diameter and show at higher magnification the typical invagination of the unit cell membrane of the Schwann cell and its close apposition to the unit membrane of the axon as described in detail by Robertson (1958). When all the nuclei associated with cytoplasm that contains either myelinated or non-myelinated fibres are included together as Schwann or neurilemmal cell nuclei, they account for about 85 per cent of all the nuclei seen.

The endothelial nuclei are easily distinguished and are illustrated in fig. 4. The elongated endothelial nucleus in the wall of the blood vessel with sections of electron dense red blood corpuscles in the lumen and the continuity of the cytoplasm of these nuclei around the blood vessels is distinctive. In the same figure is an example of the small minority of nuclei whose cytoplasm does not contain nerve fibres and that are not endothelial. It is difficult to decide whether such cells are best classified as pericytes, fibrocytes or resting macrophages, but their position is very typical in electron micrographs.

Taking the three groups of nuclei as defined above, the relative proportions in different nerves are given in Table I, from which it is clear that in

TABLE I.—COUNTS OF NUCLEI IN TRANSVERSE SECTIONS OF PERIPHERAL NERVES

	Schwann nuclei	*Endothelial nuclei*	*Other nuclei*
Mouse sural ..	138 (85%)	16 (10%)	8 (5%)
Rat peroneal ..	158 (87%)	16 (9%)	7 (4%)
Rabbit sural ..	132 (95%)	6 (4%)	1 (1%)
Rat sural ..	112 (82%)	17 (12%)	8 (6%)
Total nuclei examined 619 ..	540 (87%)	55 (9%)	24 (4%)

the nerves examined, the great proportion of cells within the perineurium are Schwann cells with an additional 10 per cent of typical endothelial nuclei varying considerably from nerve to nerve, but very distinctive in their characteristics. The third group classified as "other nuclei" includes in addition to the fibrocytes or pericytes illustrated in fig. 4 a small number of nuclei that are probably nuclei of Schwann cells, but in which the rigorous criterion of a mesaxonal connection between the pale areas in the cytoplasm and the cell surface was not definitely demonstrable, leaving a slight doubt as to whether these areas may possibly be vesicles within the cytoplasm of some other cell type.

XUM

FIG. 1.—The perineurium of the sural nerve of a mouse. The elongated nucleus of a perineural cell runs across the picture, with transversely cut bundles of collagen in the epineurium (above) and endoneurium (below). A portion of a myelinated fibre is seen at the bottom of the picture. ×6,000.

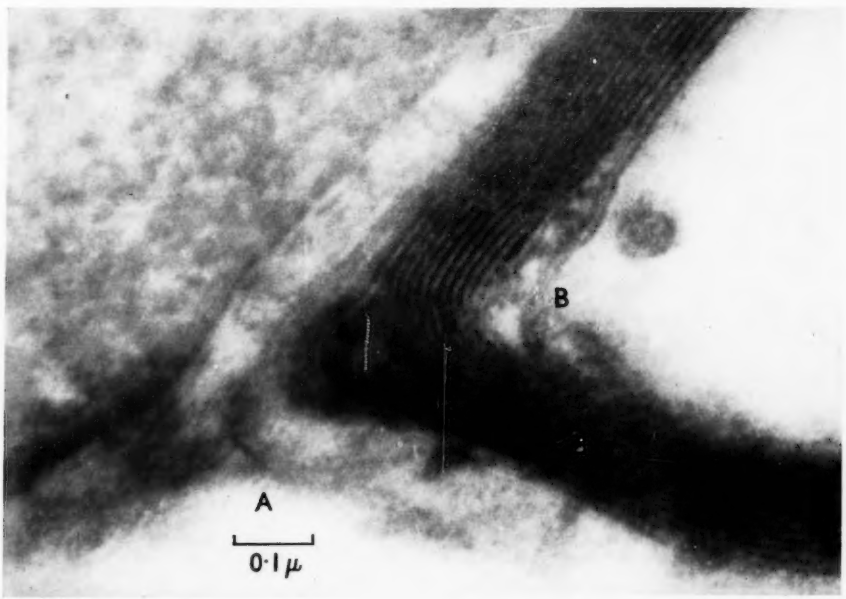

FIG. 2.—A part of a myelinated fibre and the nucleus of its Schwann cell. A marks the site of the entrant mesaxon and B that of the emergent mesaxon. ×140,000.

To illustrate article by G. Causey and A. A. Barton.

XUM

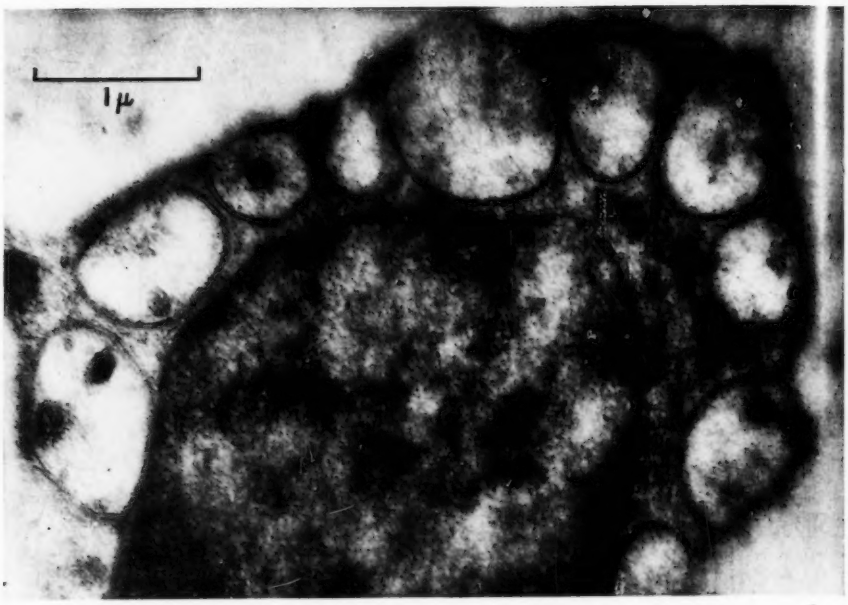

FIG. 3.—Schwann cell showing nucleus and a number of non-myelinated fibres invaginated into the cytoplasm. ×30,000.

FIG. 4.—A small blood vessel within the perineurium. Nucleus of endothelial cell at A and nucleus of fibrocyte or pericyte at B. ×6,000.

To illustrate article by G. Causey and A. A. Barton.

Discussion

If the Schwann or neurilemmal cell is accepted as any cell that enfolds myelinated or non-myelinated fibres, then the vast majority of the nuclei seen in a peripheral nerve belong to Schwann or neurilemmal cells. This leaves, particularly after the well-defined endothelial cells have also been subtracted from total cell content, a very small number of nuclei that can be looked upon as nuclei of endoneurial fibroblasts, and marks a very different distribution of the cellular content of peripheral nerve to that implied or quoted in the previous literature. It seems probable that the explanation of this divergence is based on those nuclei whose cytoplasm enfolds small non-myelinated fibres. If a purely subjective criterion is adopted for those cells whose axons are so small as to be unlikely to have been seen in ordinary histological preparations, then it was found that some 27 per cent of the Schwann cell nuclei belonged to this category, and it is suggested that this is the reason for the difference between our figures and those of Thomas (1948).

The collagen of the endoneurium is well seen in electron micrographs, but we have very rarely found a cell that was associated only with endoneurial collagen and not with a blood vessel. This would support the contention of Murray and Stout (1942) that the reticulin is produced by the Schwann cells, but the support is purely on probabilities and until further work has been done on the electron microscopy of degenerating and regenerating nerve, there is insufficient evidence to exclude the endoneurial collagen as having been deposited by perineural fibroblasts during the development of the nerve trunk. The collagen content of peripheral nerves increases during Wallerian degeneration, particularly from the 25th–100th day (Abercrombie and Johnson, 1946, 1947), and again until further work has been done on the electron microscopy of Wallerian degeneration, it is not possible to say whether this new collagen formation occurs from extremely rapid proliferation of the few fibrocytes present, or from invasion by the fibroblasts of the perineurium, or by collagenous deposition from the Schwann cells themselves.

A further consequence of this re-orientation with regard to the cellular content of peripheral nerve is also associated with processes of nerve repair. The nuclear multiplication is greater in those nerves with large myelinated fibres than in those with small myelinated fibres and is again greater than in those with no myelinated fibres. It is generally accepted by workers in this field that the rate of multiplication of the Schwann cells is greater than that of the fibroblasts (Thomas, 1948), but with the striking paucity of fibroblasts that we have seen it would appear more likely that there are different rates of mitosis among the Schwann cells themselves. One of the major problems which has arisen from recent work on the relationship of Schwann cells to axons is illustrated by the two figures, 2 and 3, which are typical of the general finding that only a single myelinated

XUM

fibre is found in relation to one Schwann cell, but large numbers of non-myelinated fibres are so found, a difference that draws direct attention to a question of what factors determine whether the developing axon or the regenerating axons remain in the structural state shown in fig. 3, or go to full myelination as shown in fig. 2.

The observations reported here are also of interest in relationship to neoplasms of nerve. With the altered emphasis on the cellular content of peripheral nerve it would seem difficult to attribute intraneural neoplasms to endoneurial fibroblasts. The only cells that we can implicate are the small percentage of pericytes which, of course, could give rise to such tumours or the perineural fibroblasts. Our observations seem to lend considerable support to the Schwann cell origin of intraneural tumours.

Summary

An examination of the cellular content of peripheral nerve fascicles has brought evidence that approximately 85 per cent of these cells are Schwann cells and less than 5 per cent may be fibrocytes, but are possibly macrophages.

This change in the classification of the cellular content is attributed to the inability to distinguish small non-myelinated fibres with the light microscope. The observations are discussed in relationship to Wallerian degeneration and neoplasms of peripheral nerves.

We would like to thank Mr. S. A. Edwards for his technical assistance, and the British Empire Cancer Campaign for financial support.

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XUM

FAMILIAL CALCIFICATION OF THE CEREBRAL BASAL GANGLIA AND ITS RELATION TO HYPOPARATHYROIDISM

BY

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FAMILIAL calcification of the brain was first recorded by Geyelin and Penfield (1929), who described multiple foci of cerebral calcification in a father and four children. The three siblings described by Fritzsche (1935) are the first recorded cases of familial calcification limited to the basal ganglia. Since then a number of cases of familial calcification of the basal ganglia have been described: in some instances calcification of the cerebrum and cerebellum has been associated. Merritt (1935) mentioned a family, but gave no details. Foley (1951) noted the condition in a mother and two daughters, Bowman (1954) in two brothers dying in infancy, Matthews (1957) in two sisters, while Camp (1948), reporting the occurrence in two sisters, commented on the resemblance of the calcification to that seen in hypoparathyroidism. Vasiliu (1940) described calcification of the basal ganglia in two sisters, both with hypocalcæmia, and this relationship was further instanced by Elrick, Albright, Bartter, Forbes and Reeves (1950) in two sisters.

Family Study

Bilateral calcification of the basal ganglia was demonstrated in a case under investigation at the National Hospital for Nervous Diseases, Queen Square (figs. 1 and 2). Following this, a search was made for similar cases in the family (fig. 3). The propositus was one of 12 siblings: 5 of these were X-rayed and 4 showed calcification of the basal ganglia. The children of 3 of these affected siblings were X-rayed and one daughter was found to have similar calcification and one son to show doubtful early calcification. In one case the calcification was unilateral, but in the other cases it was bilateral.

Clinical Features

5 of the cases showing calcification of the basal ganglia were completely symptom free at the time of the inquiry and gave no past history of significance. The remaining 2 cases (fig. 3, Cases II 11 and III 3) both had symptoms and were investigated in detail.

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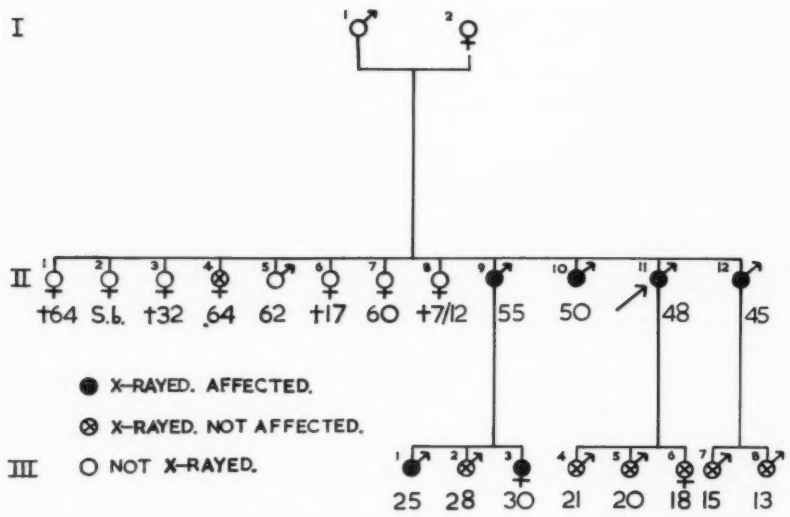

FIG. 3.—Showing related cases with calcification of the basal ganglia.

Case I.—National Hospital No. 22264 (fig. 3, Case II 11). The propositus, a man aged 48. He had a history of "fits" from infancy and remembered episodes as a child when he fell to the ground, losing control of the limbs, but with no loss of consciousness. These attacks had continued up to the time of the investigation. At the age of 26 he had developed typical *grand mal* attacks, with unconsciousness and urinary and fæcal incontinence. Aged 44 he began to experience transitory episodes of clumsiness of the right arm and leg associated with paræsthesiæ in these limbs. Four years later, aged 48, he was admitted to hospital with an eight-week history of increasingly severe throbbing headache, which on one occasion had been accompanied by vomiting and vertigo. In addition he complained of lifelong episodes when one arm and one leg felt as if they were "going to fly off": this occurred on either side and was accompanied by facial twitchings and paræsthesiæ in the affected foot.

Physical examination at this time showed a fine horizontal nystagmus, especially on looking to the left, slight slurring of the speech, and a firm non-tender skin nodule 1·5 cm. in diameter, situated immediately below the mid-point of the right clavicle.

Investigations

Blood picture, C.S.F., renal function tests, and fæcal fat—all normal. Wassermann and Kahn tests negative.

Complement-fixation and dye tests for toxoplasmosis negative (Dr. I. A. B. Cathie).

Radiology.—In addition to dense bilateral calcification of the basal ganglia (figs. 1 and 2) there was some increase in line density in the femora and the pelvis. The skin nodule below the right clavicle showed a trace of calcification.

Electroencephalography.—The alpha rhythm was asymmetrical, with very little spread forward into the left temporal region. In the occipital region, mixed with the alpha rhythm, there were runs of 5 cycles per second waves which were symmetrical. Posteriorly there was also a fair amount of fast rhythm which was nearly continuous. The degree of abnormality was considered to be not great, consistent with a long

PLATE LIII

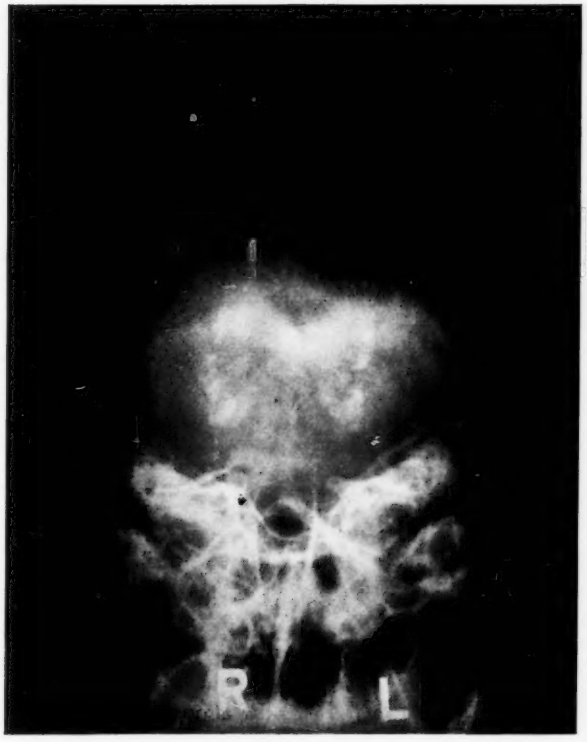

FIG. 1.—Showing the bilateral calcification of the basal ganglia in the propositus (Case I). The pineal is also calcified.

To illustrate article by P. D. Roberts.

XUM

PLATE LIV

FIG. 2.—Showing the bilateral calcification of the basal ganglia in the propositus (Case I). The pineal is also calcified.

To illustrate article by P. D. Roberts.

history of epilepsy. It was doubtful whether the asymmetry of the alpha rhythm had any lateralizing value (Dr. W. A. Cobb).

Case II.—National Hospital No. 56857 (fig. 3, Case III 3). A woman aged 30. During the family survey she was found to have bilateral symmetrical calcification of the basal ganglia. Seven years before investigation she had had an episode of severe mental depression, which responded to electroplexy. Following this there had been recurrent attacks of depression which were characterized by fits of weeping for no apparent cause.

Physical examination showed a receding chin and a prominent aquiline nose. There was a fine tremor of the outstretched hands, but no other abnormal physical signs.

Investigations

Blood picture, renal function tests and fæcal fat excretion were all normal. Wassermann and Kahn tests negative. Complement-fixation and dye test for toxoplasmosis were negative (Dr. I. A. B. Cathie).

Radiology.—Apart from the calcification in the basal ganglia, radiographs showed an unerupted bicuspid in the left upper jaw and thinning of the laminæ in both jaws, appearances suggestive of hypoparathyroidism. The long bones showed no abnormality and no subcutaneous calcification was seen.

Electroencephalography.—The record was of rather low voltage, containing a wide range of alpha-like rhythm from 12–16 cycles per second, all blocked by eye opening. There were many scattered low voltage waves at about 6 cycles per second occurring equally on the two sides. Amplitude was a little increased on over-breathing but there were no new features. The record was summarized as being a mildly abnormal electroencephalogram (Dr. W. A. Cobb).

Studies of Calcium and Phosphorus Metabolism

(i) *Method:* Both patients were placed on a strict metabolic balance regime, all food being weighed and specially prepared, with an analysis of samples for calcium and phosphorus content. Each balance period lasted six days, during which all urine and fæces were collected and analysed for calcium and phosphorus content. For calcium analysis the method of Shohl and Pedley (1922) was used: for phosphorus analysis a modification of the method of Fiske and Subbarow (1925) was used. In addition there were frequent estimations of serum calcium and phosphorus levels, using the methods of Kramer and Tisdall (1921) and Fiske and Subbarow (1925) respectively.

Four balance periods, each of six days' duration, were arranged as follows:

I. Standard diet alone.

II. Low calcium intake.

III. Standard diet, with dihydrotachysterol ("A.T.10—Bayer") 2 ml. eight hourly started two days before the balance period and continued throughout the period.

IV. Standard diet, plus ammonium thiocyanate. Thiocyanate dosage was controlled according to the serum level (Bowler, 1944): this ranged between 5·4 and 9·7 mg. per 100 ml. in Case I, and between 4·6 and 9·0 mg. per 100 ml. in Case II. The use of thiocyanate was suggested by a report of hypercalcæmia and hypophosphatæmia following thiocyanate therapy (Gubner, 1951).

(ii) *Results:* The results of these metabolic studies are shown in Table I. Both patients were in normal calcium balance and both showed a strongly positive phosphorus balance. Case I had a persistently low serum calcium level (8·6 mg. per 100 ml.) measured on three occasions, while the serum phosphorus levels were 3·9, 3·5 and 3·7 mg. per 100 ml. The corresponding levels for Case II were all normal (10·6, 9·6 and 9·4 mg. per 100 ml. for calcium, and 3·3, 3·7, and 3·5 mg. per 100 ml. for phosphorus).

XUM

TABLE I.—RESULTS OF CALCIUM AND PHOSPHORUS BALANCE PERIODS

Regime	*Case*	*Calcium intake in mg.*	*Urinary calcium mg. per 6 days*	*Fæcal calcium mg. per 6 days*	*Calcium balance over 6 days in mg.*	*Phosphorus intake in mg.*	*Urinary phosphorus mg. per 6 days*	*Fæcal phosphorus mg. per 6 days*	*Phosphorus balance over 6 days in mg.*
Standard diet ..	I	5066	1741	3608	− 283	8574	4839	2003	+ 1732
	II	3359	1183	2234	− 58	6460	3739	1402	+ 1319
Low calcium diet ..	I	1336	1862	1095	−1621	3812	3486	935	− 609
	II	906	879	1277	−1250	5224	3305	1878	− 41
Standard diet with A.T.10. 2 ml. 8 hourly	I	5205	3768	1713	− 276	7995	5564	1011	+ 1420
	II	4575	2780	1587	+ 208	7083	5045	1299	− 739
Standard diet with amonium thiocyanate ..	I	3521	1646	2679	− 804	6533	4295	1474	− 764
	II	3676	1964	2832	−1120	7128	4733	2295	− 100

Both cases showed a normal response to a low calcium intake by going into negative balance, although the urinary calcium was abnormally high in both. The concomitant reduction in phosphorus intake changed the phosphorus balance in Case I to negative, and reduced the previously positive balance in Case II to normal. Serum calcium and phosphorus levels remained unchanged throughout.

A.T.10 reduced the fæcal calcium output and increased the urinary calcium output in both cases; there was no change in the balance in Case I, and the slight positive balance obtained in Case II was probably insignificant. Both cases showed a marked rise in urinary phosphorus and a fall in the fæcal phosphorus, with a reduction in the positive phosphorus balance. The serum calcium in Case I rose to normal limits and there was no change in the level in Case II. Serum phosphorus rose in both cases.

Following administration of ammonium thiocyanate both cases went into negative calcium balance. There was an increase in urinary calcium, relative to the intake in Case I, and an absolute increase in Case II; the fæcal calcium was increased in both. The previously positive phosphorus balances were reduced, Case II returning to normal balance. Urinary phosphorus increased in both cases, again relative to the intake in Case I and absolutely in Case II. Fæcal phosphorus increased in Case II but remained unchanged in Case I. Serum calcium and phosphorus values were unchanged by thiocyanate.

Following these balance periods a parathyroid hormone preparation was given ("Parathormone-Lilly") in a dosage of 2 ml. (40 B.P. Units or 200 U.S.P. Units) intramuscularly eight-hourly for five days. The effect on urinary calcium and phosphorus output is shown in Table II. Both cases showed an increase in urinary calcium and phosphorus excretion. Case I, with an initially low serum calcium of 8·6 mg. per 100 ml., showed no significant change in serum calcium and phosphorus levels. In Case II there was a rise in serum calcium from 10·0 to 12·8 mg. per 100 ml. with a fall in phosphorus from 4·0 to 3·3 mg. per 100 ml. In a further experiment hourly urinary phosphorus excretion was determined following an intravenous injection of 2 ml. of parathormone in the fasting subject (Table III). In both cases this produced a diuresis but only a small increase in hourly phosphorus excretion, well below the normal response of approximately 70 mg. per hour (Ellsworth and Howard, 1934).

The response to an intravenous infusion of calcium was investigated, using the technique of Nordin and Fraser (1954). Following a low calcium intake for three

TABLE II.—THE RESPONSE TO INTRAMUSCULAR PARATHORMONE

		Case I		Case II	
	Day	*Urinary calcium mg. per 24 hours*	*Urinary phosphorus mg. per 24 hours*	*Urinary calcium mg. per 24 hours*	*Urinary phosphorus mg. per 24 hours*
	1	402	1142	185	493
	2	313	1152	226	367
Parathormone 2 ml. 8 hourly →	3	325	1020	302	736
	4	651	1680	576	933
	5	506	1222	525	1116
	6	492	720	540	1204
	7	470	940	630	1092
	8	440	563	466	360
	9	534	906	367	551

TABLE III.—THE EFFECT OF INTRAVENOUS PARATHORMONE ON URINARY PHOSPHORUS

		Urine volume in ml.		*Urinary phosphorus mg. per 100 ml.*		*Urinary phosphorus mg. per hour*	
	Time	*Case I*	*Case II*	*Case I*	*Case II*	*Case I*	*Case II*
	8 a.m.	30	31	78	19	—	—
	9 a.m.	30	75	74	29	22	22
Parathormone 2 ml. i.v.i. →	10 a.m.	76	105	42	17	32	18
	11 a.m.	275	185	17	18	45	33
	12 noon	265	275	18	12	48	33
	1 p.m.	43	60	89	23	38	14
	2 p.m.	50	31	110	28	55	9

days (121 mg. of calcium and 712 mg. of phosphorus daily in both patients), an intravenous infusion of 15 mg. of calcium per kilogram body weight (as calcium gluconate) was infused in 500 ml. of saline over four hours. In a normal subject, the induced hypercalcæmia depresses parathyroid secretion, urinary phosphorus and the ratio of phosphorus clearance to creatinine clearance (C_p/C_{cr}) is lowered, and the serum phosphorus rises. Both cases showed a marked rise in serum calcium to 13·4 mg. per 100 ml., with a concomitant rise in serum phosphorus (to 4·8 and 5·0 mg. per 100 ml. in Case I and II respectively). The urinary phosphorus changes in both cases were abnormal. In Case I there was a rise from 21 mg. per hour to 38 mg. per hour and the ratio (C_p/C_{cr}) rose correspondingly from 0·129 to 0·299. In Case II the urinary phosphorus excretion was initially very low at 6·7 mg. per hour and did not change significantly during the experiment: there was a slight fall in the C_p/C_{cr} ratio from 0·044 to 0·012.

DISCUSSION

These studies of calcium and phosphorus metabolism revealed a number of abnormal features. Case I showed a small but definite reduction in

serum calcium, with a normal level in Case II. Both cases were in strongly positive phosphorus balance and failed to show a normal phosphorus diuresis with intravenous parathormone, and Case I failed to respond to repeated intramuscular injections of parathormone. The response to intravenous calcium was abnormal in Case I, with no response to this test in Case II. These anomalies suggest a defect in the control of phosphorus excretion. The renal excretion of phosphorus does not keep pace with the intestinal absorption of phosphorus, nor is the phosphorus excretion response to injected parathormone normal; moreover, the hypercalcæmia induced by an intravenous infusion of calcium did not cause the expected fall in urinary phosphorus. The result of this abnormality of phosphorus excretion would be a tendency to supersaturation of the tissue fluids with calcium phosphate, and this may result in ectopic calcifications, including the brain and subcutaneous tissues.

The results suggest a relationship of these cases to hypoparathyroidism. Although classically this is associated with a low blood calcium and raised phosphorus, the patient may show normal or near normal blood levels at the time of testing (Hoesch, 1937; Emerson, Walsh and Howard, 1941; Lachman, 1941; Scott and Temple, 1949; Bakwin, Gorman and Ziegra, 1950; Cambier, 1952; Sugar, 1953; Slager, 1955). Blood levels may similarly be normal in hyperparathyroidism (Wilder, 1929; Wilder, Camp, Robertson and Adams, 1932; Jaffe, 1933).

Phosphorus retention has been repeatedly demonstrated in hypoparathyroidism and this state is usually but not necessarily associated with calcium retention, the association depending on the ratio of calcium to phosphorus in the diet (Albright and Sulkowitch, 1938; Anderson and Lyall, 1939; Emerson, Walsh and Howard, 1941; Leonard, 1946). Both cases in this investigation produced a normal negative calcium balance on a low calcium intake, whereas cases of classical hypoparathyroidism fail to go into negative balance on a calcium intake as low as 120 mg. *per diem* (Anderson and Lyall, 1939; Emerson, Walsh and Howard, 1941). A peculiar feature of this period was the high urinary calcium output in both cases. Albright and Reifenstein (1948) recorded 3 cases of hypoparathyroidism showing a high urinary calcium output with low levels of serum calcium. This they attributed to pyelonephritis in one case, but were unable to explain in the other two cases.

The response to A.T.10 was normal in both cases (Albright, 1938; Albright and Reifenstein, 1948): there was a reduction of the positive phosphorus balance, due to the induced hyperphosphaturia, and a return in Case 1 of the blood calcium to a normal level.

The phosphorus balances were also restored to normal by ammonium thiocyanate because of the increase in urinary phosphorus output. Urinary calcium also increased, resulting in negative balances. The hypophosphatæmia and hypercalcæmia seen in Gubner's cases (1951) was

not produced although the metabolic effects which Gubner proposed were actually confirmed. This discrepancy may be due to the short period of administration compared with the minimum period of administration of four weeks in Gubner's cases. The preparation was found to be too nauseating and the dosage too difficult to control (necessitating daily blood estimations) for thiocyanate to be useful in the treatment of the metabolic disorder.

An interesting feature in both the present cases was the poor response to intravenous parathormone, as well as the poor response to a prolonged course of intramuscular parathormone in one case (Case I). The intravenous parathormone test was introduced by Ellsworth and Howard (1934) and subsequently Albright, Burnett, Smith and Parson (1942) described 3 cases of hypoparathyroidism showing a subnormal response to the procedure. They suggested that the hypoparathyroidism in these cases was due to a failure of "end-organ" response, rather than a deficient production of parathormone by the gland, and called the condition "pseudo-hypoparathyroidism." Since then at least 20 similar cases have been reported, many showing in addition little or no response to prolonged intramuscular parathormone. It has been claimed that the phosphorus secretion effect of parathormone is insignificant and therefore the Ellsworth-Howard procedure is unreliable (Dent, 1953). This view is not universally accepted (de Mowbray, 1953) although more recent authors have been more cautious in their interpretation of the results of this test (Robinson, Carmichael and Cumings, 1954).

The response to an intravenous infusion of calcium in Case I was typical of that found in hypoparathyroidism (Howard, Hopkins and Connor, 1952; Nordin and Fraser, 1954): there was a rise in urinary phosphorus excretion and a rise in the ratio of phosphate clearance to creatinine clearance, instead of the normal fall in both values. It was difficult to assess the response in Case II because of the initially very low urinary phosphorus output, which did not alter significantly during the test.

In considering the relationship of these cases to hypoparathyroidism a syndrome described by Albright, Forbes and Henneman (1952) is of interest. They described a case with the clinical features of pseudo-hypoparathyroidism but with normal blood calcium and phosphorus levels. This syndrome was summarized as a-hypocalcæmic or a-hyperphosphatæmic pseudohypoparathyroidism and the rather unsatisfactory name "pseudo-pseudohypoparathyroidism" applied to it. Miles and Elrick (1955) recorded a similar case and Roche (1955) described a patient with the clinical features of hypoparathyroidism, with resistance to intravenous parathormone, but with normal blood levels of calcium and phosphorus. The two sisters reported by Matthews (1957) with calcification in the basal ganglia both had normal blood levels of calcium and phosphorus: the one case tested showed resistance to intravenous para-

XUM

thormone. The findings in familial basal ganglia calcification described in this present paper suggest that these cases also belong to the "pseudo-pseudohypoparathyroid" group.

It can be assumed that the ætiology of the calcification is the same in all the affected members of the family. The abnormality appears to be genetically determined rather than an environmental characteristic, and the family tree suggests that it behaves as a non-sex-linked dominant, appearing in two successive generations in males and females.

The problem remains of the relationship of the symptoms in these 2 patients to the calcification in the basal ganglia and the metabolic disorder. Major epileptic attacks have frequently been described in hypoparathyroidism, the literature of this association being well reviewed by Sugar (1953). The episodes in Case I which involve two limbs suggested focal attacks. This may also occur in hypoparathyroidism (Sutphin, Albright and McCune, 1943; Simpson, 1952; Robinson, Carmichael and Cumings, 1954). The more recent onset in this case of headache and vomiting suggested the presence of an intracranial space-occupying lesion. A similar picture has been recorded in hypoparathyroidism, Grant (1953) collecting 28 similar cases, 16 of whom had generalized convulsions.

Mental changes were noted in both Cases I and II, being the only feature in Case II. A variety of mental change has been described in hypoparathyroidism, ranging from anxiety and depression to a frank psychosis (Kowallis, 1941; Blum, 1941; Cantor and Scott, 1942; Simpson, 1952; Sugar, 1953). Mental changes have also been noted in hypoparathyroidism associated with basal ganglia calcification (Camp, 1947; Chavany, van Bogaert and Houdart, 1949; Schottstaedt and Gordan, 1951; Robinson, Carmichael and Cumings, 1954), and in pseudohypoparathyroidism (Berardinelli, 1951). The case of pseudo-pseudohypoparathyroidism described by Miles and Elrick (1955) was mentally retarded, and one of the two sisters with basal ganglia calcification described by Matthews (1957), probably related to this group, showed a low grade dementia with emotional lability.

The mild electroencephalographic changes observed in both cases may again be related to hypoparathyroidism (Odoriz, del Castillo, Manfredi and de la Balze, 1944; Gotta and Odoriz, 1948; Gotta, 1951; Wise and Hart, 1952; Sugar, 1953; Grant, 1953; Hansted and Brandt, 1953), to pseudohypoparathyroidism (Peterman and Garvey, 1948; Moehlig and Gerisch, 1950; Berardinelli, 1951), and to pseudo-pseudohypoparathyroidism (Miles and Elrick, 1955).

It is remarkable to note the absence of any clinical evidence of a lesion in the basal ganglia, despite the heavy calcification in this area. However, in the many cases of classical hypoparathyroidism with calcification of the basal ganglia described, there is no account of any clinical evidence of extrapyramidal involvement. All the cases showing such signs belong in

fact to the pseudohypoparathyroid group (Robinson, Carmichael and Cumings, 1954), the pseudo-pseudohypoparathyroid group (Trufant and Seaman, 1952), or to the familial group (Matthews, 1957).

Treatment

A.T.10 reduced the positive phosphorus balance in both cases. Both were given 1 ml. daily, a dosage which was subsequently reduced to 0·5 ml. daily. On this treatment the serum calcium remained between 10 and 11 mg. per 100 ml., and the phosphorus between 3 and 4 mg. per 100 ml. in both cases. With this treatment Case I showed a marked improvement in his clinical condition. There were no further fits nor episodes involving loss of control of the limbs. The headache was reduced to an occasional dull sensation on waking, and mentally he was greatly improved, returning to his old work. This improvement has been sustained with continued treatment.

Case II showed less marked improvement. Her depression responded during treatment and she was able to return to work. Unfortunately she soon defaulted and it was not possible to assess her response over a long period of treatment.

Summary

(1) Calcification of the cerebral basal ganglia is described in five members of one family, with probable calcification in a sixth. The condition appears to be inherited as a non-sex-linked dominant.

(2) In Case I the calcification was associated with major epileptic attacks and episodes of loss of control of the limbs, with a more recent onset of headache and vomiting. Case II had a history of recurrent severe mental depression. The other affected members of the family were symptomless.

(3) A metabolic investigation of the two patients with symptoms showed a positive phosphorus balance in both cases; a low serum calcium corrected by dihydrotachysterol in Case I; an abnormal response to intravenous parathormone in both and to prolonged intramuscular parathormone in Case I; an abnormal response to intravenous calcium, suggestive of hypoparathyroidism, in Case I and an equivocal response in Case II.

(4) The metabolic findings can be explained by a defect in the control of phosphorus excretion by the kidneys. This may result in supersaturation of the tissue fluids with calcium phosphate and be related to the ectopic calcification.

(5) This condition of familial calcification of the basal ganglia appears to belong to the group of pseudohypoparathyroid cases described by Albright, with normal or almost normal blood calcium and phosphorus levels: the so-called "pseudo-pseudohypoparathyroid" group.

XUM

(6) Case I showed an excellent response to treatment with dihydrotachysterol (A.T.10), with almost complete alleviation of symptoms. A less convincing response was obtained in Case II.

I wish to thank Professor J. N. Cumings for his continual encouragement, Mr. Harvey Jackson for allowing access to cases under his care, Mr. P. C. Carey for drawing my attention to this condition, the Lysholm Radiological Department and the Photographic Department of the National Hospital for Nervous Diseases, Queen Square, for the photographs, and Dr. H. B. May for reading the manuscript.

This paper is based on material incorporated in a thesis for the M.D. examination of the University of Leeds.

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XUM

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XUM

FASCICULI PROPRII OF THE SPINAL CORD IN MAN

Review of Present Knowledge

BY

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In 1955 we published a review of what is known about the anatomy of the long descending tracts in man. In the present review we are concerned with what is known about the anatomy of the fasciculi proprii of the human spinal cord. Under this heading we are considering all those fibres that cannot be suitably included under the headings of long descending and long ascending tracts. We will not be publishing a review of what is known about the anatomy of the long ascending tracts in a separate paper, as this material will accompany original observations in a series of papers. The first of these, including the literature on the course of the spino-cerebellar tracts in man, has been published by Smith (1957).

The fasciculi proprii of the cord constitute what Edinger (1885) called "den Eigenapparat des Rückenmarks" (the spinal cord's own apparatus). The great importance of this "apparatus" is not always fully appreciated. This system of fibres mediates at least all those functions that continue after the spinal cord has been transversely divided: that is to say, it mediates all automatic functions of the spinal animal, vasomotor, sudomotor, bowel functioning, genito-urinary functioning, and the co-ordination of the musculature of the trunk and limbs. The fasciculi proprii tend to be neglected more than the long tracts because they are made up of a large proportion of small fibres, and small fibres are not so easily made manifest by histological or physiological methods. However, the number of these fibres is probably an indication of their importance. An idea of the relative density of distribution of such fibres is obtained from fig. 1, which is taken from a paper by Tower, Bodian and Howe (1941).

Comment on the Investigation of Tracts

The main features of the course of a tract are determined largely by following myelogenesis in the embryo, by the application of the Golgi

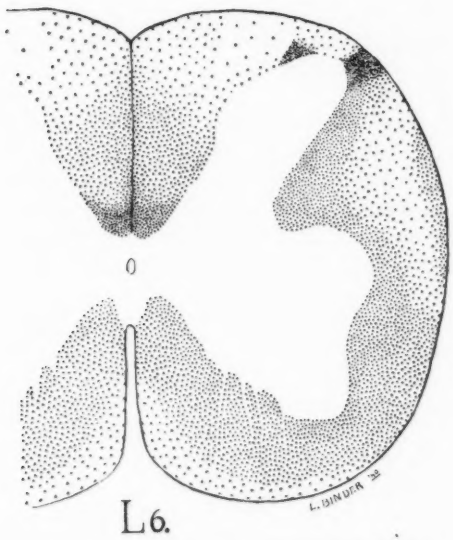

Diagram representing the relative density of distribution of fibers surviving in the white matter of the completely isolated segment of spinal cord.

FIG. 1.—Reprinted with kind permission of the Editor, and Tower, Bodian and Howe; from *J. Neurophysiol.* (1941) **4**, 388.

method to embryos and to newborn animals, and by following tracts which are degenerating subsequent to an experimentally induced or naturally occurring lesion. In man, the last has been the most important method. When this knowledge of normal anatomy obtained from pathological material is considered, it is necessary to keep certain points in mind. Conclusions are most reliable when they are based on actual staining of the degenerating fibres, a feature of the Marchi method or of silver impregnation; they are less reliable when they are based on techniques which leave the degenerating fibres unstained, as with the Weigert-Pal method. It follows that when fibres have been clearly demonstrated by positive staining, then a failure to show these fibres when a negative stain is used provides no evidence of their lack of existence. It should further be remembered that the resultant picture is greatly dependent on the duration of time between the occurrence of the lesion and death. If this length of time is very long, all fibres of the relevant tract will have disappeared.

Degeneration studies have not been of such use for the fasciculi proprii as they have been for the long ascending and descending tracts. In the

XUM

fasciculi proprii many of the fibres are short, many are of small diameter, and many are unmyelinated. Also, the fibres of the fasciculi proprii are much intermingled with the fibres of other tracts. Although all tracts in the spinal cord are mixed, it is only immediately round the grey matter and within Lissauer's tract that the fibres of the fasciculi proprii are congregated in sufficient density to appear to the anatomist as that kind of collection of fibres which he likes to see when he has named a certain group of fibres—a tract. This scattering of the fibres in the spinal cord makes their degeneration inconspicuous—unlike that seen in the large ascending or descending tracts—following a lesion of a certain part of the cord.

When the anatomy of a tract is worked out by tracing fibres degenerating subsequent to a lesion, it is important to remember that information is obtained only about the fibres that have been affected by the lesion. Obviously this limitation of the method of examining tracts does not occur with a large tract originating in the encephalon and examined in the spinal cord. For instance, an encephalic lesion involving the whole cortico-spinal tract will cause degeneration in all the fibres of the tract in the spinal cord; and the resulting pattern of degeneration taken at any spinal segment is indeed the pattern of the entire extent of the cortico-spinal tract at that level. Very different is the result of a lesion of a tract which originates in the spinal cord. For in this case only those fibres of the tract that have been separated from their cells of origin by the lesion will degenerate. If, for instance, one examines the spino-tectal tract in a case with a transverse cord lesion at the seventh cervical segment, the picture of the degeneration in this tract at the first cervical segment is of the spino-tectal fibres originating caudal to the seventh cervical segment; those originating above the lesion will not be demonstrated. With regard to the short chains of fibres which are a main feature of the fasciculi proprii, this limitation of the method of defining the extent of a tract by means of degeneration is particularly evident; an adequate conception of the whole tract could be obtained only from a composite picture made up from lesions at all levels. It scarcely needs saying that such evidence has not been collected. Even though this limitation of the method is evident, it is apparent from reading the literature on some parts of the anatomy of the fasciculi proprii and of the posterior root fibres, that some workers have neglected it.

There are some other inevitable limitations of the method of studying tracts by means of degeneration studies. It is known that even within the central nervous system all fibres do not degenerate at the same time following a lesion, and the debris of degeneration is not removed from all fibres at the same time. The difference in time of both the rate of degeneration and the rate of removal of the debris of degeneration are related to the species of animal investigated and to the size of the fibres, to mention only the two most important factors. An important review of this aspect of degeneration studies can be found in the thesis by van

XUM

Crevel (1958). He emphasizes that as at any chosen time "degeneration in a tract is always partial, and when the last fibres are degenerating, the first have already been resorbed," it is advisable always to examine a degenerating tract at, at least, two different times after the infliction of the lesion. It need hardly be said that this kind of information has rarely been obtained from experimental studies in small mammals, and more rarely has it been obtained from natural lesions occurring in man.

Two criticisms of the work of the earlier neuro-anatomists may be made; they apply to most of their work on the fasciculi proprii and particularly to their work on the cells of origin of the ground bundles. The earlier anatomists were not accustomed to present their evidence. They made definite statements and sometimes gave a few drawings. It seems to us that these statements cannot be accepted as a basis of our knowledge of anatomy. This is certainly not meant to imply that the statements of the anatomists of the nineteenth century are wrong; it means that much of their work needs confirmation before it can be permitted to pass into the corpus of things definitely known. Further, it is difficult to find out from the work of most of these anatomists what parts of their investigations were done on what species and what parts were done on man. This is not always so; Kölliker worked on the human fœtus as well as on other embryos, using the Golgi technique; he, Ziehen, and von Lenhossék always made it clear what species they were referring to and whether it was the embryo, fœtus or the adult form. From the publications of Golgi, van Gehuchten, and Ramón y Cajal, however, it is difficult to discover for what species the statements made are considered to apply.

The other criticism that should be kept in mind when reviewing the early work on the cells of origin of these tracts is this: the first workers, such as Ramón y Cajal, von Lenhossék, and Kölliker, were occupied with establishing the cells of origin of all the fibres constituting the various columns of the cord; for instance, they would try to determine the location of the cells of origin of the fibres of the lateral column. But the cells of origin of the tracts within the columns, such as the spino-cerebellar or the anterior ground bundle, were not usually what they were investigating. Since their time not much work has been done to sort out the cells of origin of the various tracts that we recognize today. In what follows we have attempted to extract from the accounts of the earlier workers the statements that can be taken to refer rather to the ground bundles than to the fibres of other tracts arising in the spinal cord. Yet it must be realized that the sections of this review on the cells of origin of the ground bundles should be regarded rather as likely suggestions than as known fact.

Terminology

Our policy with regard to terminology has been to use, wherever possible, that advocated by the Sixth International Congress of Anatomists held in

XUM

Paris on July 24, 1955. It was agreed by the Nomenclature Committee of the Congress that Latin names might be translated into living languages. Accordingly we have used English names in most cases; but sometimes we have retained the Latin name—for instance, substantia gelatinosa—where the Latin name is always preferred to its English translation. And we have retained the name "fasciculi proprii" for the fibres under review, as there is no suitable English equivalent. Sherrington's name "proprio-spinal fibres," or van Gehuchten's "spino-spinal fibres," might be suggested. But it seems to us that a name which includes the term "spinal" is undesirable, as it allows the reader to forget—as is frequently done—that these fibres connect not only one part of the spinal cord with another but also the spinal cord with the brain-stem.

Where the International Congress of Anatomists supplied no names, we have chosen them somewhat arbitrarily. For the principle to which we adhered in naming the long tracts—giving the origin and termination—breaks down when applied to the fasciculi proprii. This is perhaps as it should be; for these fibres should not be thought of as originating in a single small region—such as the red nucleus or the vestibular nuclei—and running to a similar region—such as the inferior olive; they are rather to be conceived as links, connecting up many regions cranial and caudal, often ipsilateral and contralateral, to the region of their origin. Synonyms will be given when each name is first used, so as to help those using other terminologies and those using French and German literature.

The following tracts or bundles of fibres will be considered:

(1) The ground bundles: Anterior ground bundles
Lateral ground bundles
Posterior ground bundles
(2) Lissauer's tract.
(3) Cornu-commissural tract.
(4) Comma tract.
(5) Septo-marginal tract, including the oval field and the triangle of Gombault and Philippe.
(6) Anterior septal fibres of Hoche.
(7) Anterior commissure.
(8) Posterior commissure.
(9) Intrinsic fibres of the grey matter.

Reference will be made to species other than man only where the knowledge concerning man is inadequate; unless it is specifically stated not to be so, all statements refer to man.

The ground bundles will be considered under the three headings, anterior, lateral, and posterior. There is good reason to consider the posterior ground bundle separately from the anterior and lateral, but the

separation of the rest of the ground bundles into anterior and lateral is somewhat arbitrary. We have, however, followed the usual practice in doing this, mainly because it facilitates the reading and digesting of this large amount of knowledge.

There exist many ways of classifying the various groups of fibres that are usually included in the ground bundles. Some workers use the term ground bundles to designate only those fibres that lie immediately adjacent to the grey matter. We consider that this is an undesirable practice, as it obscures the fact that these fibres are scattered throughout the white matter of the cord, intermingled with other tracts and bundles. And throughout the white matter, to quote Tower (1937) on the puppy, these "unmyelinated and small myelinated fibres are present in enormous numbers."

As most of the earlier work on this subject was published in German, the following German names need elucidation. The anterior and the lateral ground bundles are the Vorderstranggrundbündel and the Seitenstranggrundbündel; they are called together the Vorderseitenstrangreste. Medial to the Seitenstranggrundbündel is the seitliche Grenzschicht, or lateral limiting layer. Flechsig (1876) introduced the term Seitenstrangrest to describe a region of the cord that includes the tracts of the seitliche Grezschicht, the Seitenstranggrundbündel, and the lateral system of the Seitenstrangrest; the latter is now known to contain fibres of the spino-cerebellar and spino-thalamic tracts and fasciculi proprii.

The Anterior Ground Bundle

The anterior ground bundle will be considered to consist of all fasciculi proprii fibres of the white matter situated between the anterior median fissure and the most lateral of the anterior roots (*see* fig. 2). It will be

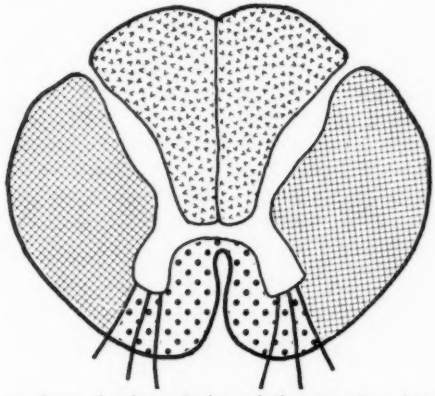

Fig. 2.—Diagram to show the boundaries of the anterior, lateral, and posterior ground bundles.

XUM

considered as including the fibres of all the tracts which have been named as follows: the ascending and descending sulco-marginal tracts of Marie, the commissural tract of Ramón y Cajal, the anterior part of the cornu-marginal tract, and the fibres belonging to the fasciculi proprii system running within the median longitudinal bundle. It will be considered as including also the fasciculus intermediolateralis of Loewenthal, even though the fibres of this tract spread into the lateral column.

Cells of Origin

The cells of the vertebrate spinal cord were classified by Golgi, Kölliker, Laura, and Ramón y Cajal as falling into two groups: the radicular cells, giving rise to the anterior roots; and the column cells ("cellules des cordons" or "Strangzellen") giving rise to the long ascending tracts and the fasciculi proprii.

There are two well-known papers on the cells of the human spinal cord —by Massazza (1924) and by Rexed (1952). Rexed's description and classification of the cells is most useful and he provided an equally good discussion of the subject. As these workers were concerned solely with the cells and not with locating the cells of origin of the various tracts, their work is not quite relevant to the subject under review, and it will therefore be mentioned only rarely in the rest of this review.

Man.—Von Lenhossék (1889), using Golgi and Weigert preparations, studied mainly the lumbar and more caudal segments of the thoracic region of man. He found no fibres of the anterior column having their cells of origin in the posterior horn. The fibres running near the anterior median fissure originate mainly in the middle region of the grey matter, between the anterior and the posterior horns, and partly in the anterior horns, in their most posterior region. The fibres running at the border between the anterior and lateral ground bundles, that is in the region traversed by the anterior roots, also originate in the middle zone and the anterior horns. The cells of origin are small and star-shaped.

Ziehen (1899) stated (although his evidence was not presented) that the cells of origin of the anterior ground bundle are situated in the medial part of the anterior horn and in the substantia intermedia lateralis. (This part of the grey matter was called the tractus intermediolateralis by Clarke; before the revision of anatomical nomenclature at Paris in 1955 it was usually called the zona or pars intermedia. In Ramón y Cajal's terminology it is the noyau du cordon antéro-latéral and probably includes his noyau gris intermédiaire; it is the tractus cellularum intercornualis lateralis of Jacobsohn, zone intercornuelle du cordon latéral of Massazza, and Lamina VII of Rexed.) Unlike von Lenhossék, Ziehen considered that a few of the fibres take origin from cells of the nucleus proprius of the posterior horn (nucl. magnocellularis centralis, nucl. centro-dorsalis, nucl. spino-thalamicus, nucl. cornus posterioris of Waldeyer, Innenzellen des

Hinterhornkopfes of Ziehen, basal group of nucl. magnocellularis centralis of Foerster and Gagel). It is important to note that some of the cells giving origin to these intrinsic fibres in the anterior horn are only slightly smaller than the cells of origin of the anterior roots; for not all radicular cells are large. Ziehen described the cells of origin of the anterior ground bundle as being polygonal and spindle-shaped.

According to Collier and Buzzard (1903), the cells of origin of those fibres ascending in the median longitudinal bundle (posterior longitudinal bundle, fasc. commissurae posterioris) "appear to take their origin in the ventral root of the same side."

Branching of the axon, according to von Lenhossék, is rare in man. When it occurs, the axon divides into two or three equal divisions. Usually the two branches remain in the same column, but there are some with one branch in the lateral column and one or two in the anterior column.

Other species.—The account that follows is based mainly on the work of Ramón y Cajal (1899). Usually he worked on the embryo of the chicken, confirming his findings on the embryos of the mouse, rat, rabbit and calf. The cells of origin of the anterior ground bundle are probably situated in all parts of the grey matter and are present throughout the length of the spinal cord. In the anterior horn, the cells of origin lie near the periphery not far from the white matter. In the lateral horn, they are in the interstitial nucleus and in the more anterior parts of the nucleus lateralis (nucl. intermedio-lateralis). In the posterior horn there are some groups of cells giving rise to axons of the anterior ground bundle. The axons of these cells which cross the mid-line do so in the anterior commissure.

Ramón y Cajal separated off the medial and most internal part of the anterior ground bundle, naming it the commissural tract; the cells of origin of the fibres of this part he called commissural cells. This name was chosen as all the axons of this tract are crossed, and they all cross the mid-line in the anterior commissure. The tract is well-developed in all vertebrates. He found cells giving origin to the fibres of this tract situated in all parts of the grey matter "except, perhaps, in the substantia gelatinosa [substantia gelatinosa Rolandi] and in the nucleus dorsalis [Clarke's column]." The cells are commonest in the anterior horn, being congregated postero-medial to the antero-medial nucleus of the anterior horn; here they constitute the anterior cornu-commissural nucleus (Ramón y Cajal's anterior commissural nucleus); this nucleus gives rise also to axons running outside the commissural tract, many running in the rest of the anterior ground bundle. The interstitial nucleus also gives rise to fibres of the commissural tract. Ramón y Cajal described the cells of the nucleus giving rise to the fibres of the commissural tract as star-shaped and fusiform. They vary greatly in size, though most of them are smaller than the majority of radicular cells. It is nevertheless important to realize that they

XUM

cannot be distinguished from motor cells by size, as some of them are as large as fairly large motor neurones, and as some motor neurones are fairly small. In the days when these cells of origin of the fasciculi proprii were being described, it was unknown that gamma fibres running to the muscle spindles had their cells of origin in the anterior horns.

According to Ramón y Cajal the dendrites of the cells in the anterior cornu-commissural nucleus, which give rise to the fibres of the commissural tract, run in all directions and they intertwine with those of their opposite numbers on the other side of the cord in front of the central canal in the anterior commissure.

Kölliker (1891*a*) found in the embryos of the ox, sheep, goat, pig, dog, cat, and rabbit, that most of the cells of origin of the ascending fibres in the anterior column are situated in the anterior horn and mainly within the anterior medial group of cells. The axons of these cells cross the mid-line in the anterior commissure.

Golgi[1] (1880, 1890, 1903) described cells in the posterior horn which give rise to axons passing through the anterior commissure to run in the contralateral anterior column; the species was not mentioned. Winkler (1918) also stated—although no evidence was given and the species was not mentioned—that the cells of origin of the ascending fibres of Marie's sulco-marginal tract (short anterior tract of anterior columns) are in the posterior horn; he considered that they are the apical cells of the posterior horn (pericornual cells, postero-marginal cells, pericornual magnocellular cell column of Jacobsohn and of Papez) and the cells of the substantia gelatinosa. Pollak (1935), who also presented no evidence, stated that the cells of origin of the anterior ground bundle are in the nucleus cornu-commissuralis anterior, the anterior paracentral nucleus (Massazza), the nucleus proprius of the anterior horn, and that the fibres arise also from small cells disseminated in the anterior column.

Course

Man.—The course of the anterior ground bundle was worked out by Flechsig (1876) and Bechterev (1885, 1899) in human fœtal material, and by Collier and Buzzard (1903) on 12 cases of transverse lesions of the cord in adult man. A group of fibres of the anterior and lateral ground bundles has been considered as a separate group and named the fasciculus intermedio-lateralis of Loewenthal. The course of these fibres has recently been investigated in man by Sie Pek Giok (1958).

The anterior ground bundle should be conceived as consisting of axons running in all directions—ascending and descending, ipsi- and contra-

[1]The dates given here for Golgi's work are 1880 and 1903; Golgi first reported the work in 1880 at the 3rd Italian Psychiatric Congress held at Reggio Emilia; it was published in the Anatomische Anzeiger in 1890; and it was reprinted in his Opera Omnia in 1903.

lateral; further, any one axon may have ascending and descending divisions, and these divisions may run ipsi- or contralaterally. In addition, the axons give off collaterals throughout their course. The anterior ground bundle is present throughout the length of the cord; it is most developed in the cervical and the lumbar enlargements. Most of the bundle is situated near the grey matter of the cord; and following the usual anatomical principle the shorter fibres lie nearest to the grey matter, the longest fibres more peripherally. Barbacci (1891) found in his case of a transverse cord lesion that the descending fibres are particularly numerous round the anterior roots as they emerge from the grey matter.

The length of the fibres varies between fibres running all the way from the caudal part of the cord into the mid-brain and fibres of less than one segment's length; the short fibres predominate. Winkler (1918) stated that the fibres of this bundle in the thoracic cord ascend for six or seven segments. In 6 cases of cordotomy, Sie Pek Giok found the intermediate zone of the anterolateral column to be particularly rich in descending fibres of this system. These fibres varied in length between those running for two segments and those descending from the lower cervical or upper thoracic segments to the lumbar enlargement; most of them descend for three or four segments. Collier and Buzzard observed that when a transverse lesion of the cord is in the lower thoracic region, there are few ascending fibres in the anterior ground bundle; there are more when the lesion is in the cervical enlargement. More evidence on the length of the fibres of the anterior ground bundle has not been recorded.

From the work of Ramón y Cajal (1890, 1899), Hoche (1896*a*), Bechterev (1899), Ziehen (1899), Collier and Buzzard (1903), and Bing (1905), it is known that the anterior ground bundle contains both ascending and descending fibres. Ziehen considered that after transverse lesions of the spinal cord there are along the medial edge of the anterior horn as many fibres degenerating in an ascending as in a descending direction. Bing concluded from the study of a case of anterior poliomyelitis affecting the lumbar cord from the third to the fifth segments that most of the fibres of the bundle at this level are ascending.

Fasciculi proprii fibres run within the median longitudinal bundle—as was first shown by Flechsig (1876). The ascending fibres within the median longitudinal bundle ascend into the mid-brain, as do some of the fasciculi proprii fibres lying outside the median longitudinal bundle. The course of the ascending fibres not forming a part of the median longitudinal bundle is as follows, according to Collier and Buzzard (1903). "In the first cervical segment they sink towards the medial aspect of the ventral horn. . . . When the pyramid commences these fibres lie between the pyramid and the remains of the ventral horn, being here joined by fibres of the same system that have retained a position close to the lips of the ventral fissure throughout their course in the spinal cord." The course of

XUM

the fibres within the median longitudinal bundle is as follows. They keep parallel to the central canal as it passes posteriorly in the ascent; they lie along the median raphe. Within the median longitudinal bundle at the level of the medulla oblongata, the fibres ascending from the anterior ground bundle lie posterior to those ascending from the lateral ground bundle. These anterior ground bundle fibres run to the posterior region of the medial part of the reticular substance. According to Collier and Buzzard, in the reticular substance "they are so arranged that the fibres from the lower parts of the cord lie dorsal and mesial to those from the higher segments of the spinal cord."

Other species.—The commissural tract was separated from the rest of the anterior ground bundle by Ramón y Cajal; it is that part which lies anterior to the anterior commissure, lateral to the long descending tracts abutting against the median fissure, medial to the anterior horn, and posterior to other fibres of the anterior column, from which it is not in fact separated. Ramón y Cajal considered the ascending fibres of the median longitudinal bundle as a "bulbar prolongation" of the commissural tract, although he wrote that the median longitudinal bundle also contained fibres of the anterior ground bundle which did not lie within the commissural tract. The deeper fibres within the median longitudinal bundle were found in the mouse to be those from the commissural tract. The first worker to investigate the fasciculi proprii by performing two transverse sections of the cord and examining the portion between the two sections at suitable times after this operation was Grünbaum (1894). His evidence was presented merely as an inadequate diagram, and his work and conclusions are open to so many criticisms, that the first valuable evidence on the course of these fibres in species other than man is Ramón y Cajal's.

Ramón y Cajal (1899) found that most of the anterior fibres of the ground bundle are ipsilateral, apart from most of the fibres of the commissural tract, which are contralateral. That these latter fibres run contralaterally was confirmed for the guinea-pig by Bok (1928). In those species investigated by Ramón y Cajal, the axons divided within the grey matter into two or three more or less equal divisions. The subsequent distribution of the two divisions conforms to certain patterns: the two divisions may remain ipsilateral, one branch running in the part of the anterior bundle known as the commissural tract and the other branch remaining in the anterior ground bundle outside the commissural tract; one branch may run in the contralateral commissural tract, the other branch remaining ipsilateral in the rest of the anterior ground bundle; or the two branches may both remain outside the commissural tract, the one running contralaterally and the other ipsilaterally. When the axon divides into three divisions, each may run in a different column. A common variation is for two of the branches to run in the anterior columns of the two sides while the third runs in the lateral column. All divisions which cross the mid-line do so in the

anterior commissure. The fibres of the commissural tract divide into two equal or unequal branches, one ascending, the other descending. Most workers have found that the branching of axons is most easily seen in the chicken embryo. Ramón y Cajal showed that the fibres taking origin near the substantia intermedia centralis mostly run contralaterally. Some of these axons also divide, the one division running in the anterior ground bundle, the other in the posterior ground bundle. He also found others divided into three branches, of which one ran into the posterior horn, one remained in the ipsilateral ground bundle, and the third crossed via the anterior commissure to the contralateral commissural tract.

With regard to the length of the fibres of this tract, Probst (1899) found in the cat and the dog that some fibres connect the anterior horns of the thoracic segments with those of the lumbar and sacral segments. Rothmann (1899) found in the dog that fibres originating in the sacral and lumbar regions of the cord go to all levels of the cord, but do not ascend into the medulla oblongata. Sherrington and Laslett (1903) found in the cat and dog that the longest ascending fibres of the anterior ground bundle extend from the caudal regions of the cord to reach the seventh cervical segment. More recently van Beusekom (1955) has carried out an excellent investigation of the anterior and the lateral columns of the cat. He found that the fibres of the anterior ground bundle surrounding the anterior horn do not extend more than a segment cranially or caudally to their cells of origin; such short fibres are ascending and descending in equal numbers. He did not find many long descending fibres in this system. He found also that the fibres of the median longitudinal bundle that lie nearest to the grey matter are all intrinsic cord fibres. In the more caudal levels of the cord, for example, at the first lumbar segment, the posterior two-thirds of the median longitudinal bundle consists entirely of descending intrinsic fibres.

Although the usual rule obtains, the shorter fibres lying nearest the grey matter, the longer more peripherally, it is known that in the monkey there are some large myelinated fibres of this bundle situated very near the grey matter; whether these are short or long fibres is unknown.

Terminations

Man.—Since the discovery of collaterals by Golgi and Ramón y Cajal, one must have a conception of fibres which have collaterals as not ending in one place but as having multiple terminations due to the widespread distribution of these collaterals. This may well mean that there is no tract consisting of fibres leading merely from one place to one other place; possibly all or nearly all axons make multiple connexions.

The number and distribution of the collaterals of this tract (and of all tracts) certainly needs further investigation. According to von Lenhossék (1892), the main mass of the fibres of the grey matter is made up of

XUM

collaterals. Little attention is paid to these questions today, mainly, it seems, as very few anatomists use the Golgi technique.

Most of the earlier workers found that the fibres of this tract give off many collaterals, both in the grey and the white matter. Von Lenhossék (1892) found that the collaterals of the fibres running in the commissural tract go to the anterior cornu-commissural nucleus; others penetrate deeper into the anterior horn and run to the medial group of anterior horn cells. In man, very few of them run in the anterior commissure. The more laterally situated fibres have collaterals running to the anterior horn cells. The collaterals tend to occupy the regions between the groups of cells in the anterior horn, regions relatively poor in cells. There are many collaterals in the region where the anterior and lateral ground bundles join, where the anterior roots traverse the white matter. There are also collaterals surrounding the anterior horns in arcs. These findings have been confirmed by Kölliker (1896), Ziehen (1899), and Bechterev (1908). Kölliker (1891) stated also that the fibres constituting the median longitudinal bundle give off many collaterals; Ziehen and Bechterev considered that the collaterals terminate around the motor cells of the anterior column.

The dendrites of the cells of the anterior ground bundle traverse the anterior commissure; many of them reach the opposite anterior horns and many run along the edge of the opposite anterior horn, remaining between the white and grey matter.

The fibres of the anterior ground bundles terminate throughout the length of the cord; and a large portion continue out of the cord into the medulla oblongata. Within the cord, they terminate by passing into the grey matter, mainly in the antero-lateral part of the anterior horn. The fibres ascending into the encephalon were studied particularly by Bechterev (1885, 1899). He found that some of the fibres of this bundle terminate between the two olives and some go to the superior olive. Some fibres could be traced to about half-way along the pons where they ended in the reticular nuclei near the median raphe. Other fibres, lying lateral to the median longitudinal fasciculus, go to the nucleus centralis superioris. And some of them cross the median raphe. The fibres of the tract that run in the median longitudinal fasciculus terminate in the posterior region of the medial part of the reticular substance. Collier and Buzzard traced some of the fibres to the nuclei of the third, fourth and sixth cranial nerves and to the nucleus of Darkschewitsch. Bechterev (1899) found that collaterals run to these nuclei and also the twelfth cranial nucleus. The ascending fibres that do not run within the median longitudinal fasciculus are said by Collier and Buzzard to enter the olive, the inferior peduncle and the mesial fillet. Some run to the medial part of the reticular formation, medial to the hypoglossal nerve; many go to the nucleus centralis inferioris. Such fibres are really better thought of as spino-reticular.

XUM

From Golgi preparations, it appears that the bundle links up the anterior horns and then continues into the brain to fulfil the same function with regard to the cranial nerve nuclei.

Other species.—Kölliker (1891*a*) found in the ox embryo that when these fibres terminate they break up into two or three divisions. He considered that the fibres that cross in the anterior commissure terminate in the anterior horns, in relation to the motor neurones. He thought it possible that some also went to the contralateral posterior horns.

In all species, Ramón y Cajal found that the axons of the anterior ground bundles are very rich in collaterals. Those of the part of the bundle named by him the commissural tract leave the parent axons in the grey matter, in the anterior commissure, and in the column which the axon attains after it has crossed the cord. Kölliker agrees in finding a great many collaterals of these axons. The collaterals of the commissural tract run to the motor neurones of the anterior horns, to the other commissural cells both of the same and of the opposite side, to the substantia intermedia lateralis, and to the posterior horn of the same side.

Intermingling of Tracts

Man.—Near the grey matter all fibres running longitudinally belong to the ground bundles; as the distance from the grey matter is increased, these fibres are intermingled with the fibres of all other tracts of the anterior column.

Myelination, Number and Size of Fibres

Man.—As is well known, Flechsig (1876) was the first to study myelination in a systematic manner. The earliest fœtus in his series was 5 months old (25 cm. fœtus). At this stage Flechsig found myelination already present in the anterior ground bundle; it was situated in its lateral part near the grey matter of the anterior horn. It was the only region of the cord to show myelination. Earlier fœtuses were studied by Hösel (1899). He found that the first fibres of the medulla oblongata to become myelinated are those of the median longitudinal bundle; and he thought it probable that the fibres are those ascending from the anterior ground bundle. Later, Keene and Hewer (1931) found that by the fourteenth week a few fibres of the median longitudinal bundle in the medulla oblongata "show fine myelination." All workers agree that the ground bundles are the first fibres of the cord to myelinate, and that the anterior ground bundle myelinates before the lateral. Keene and Hewer confirmed that myelination starts in the anterior ground bundle at the fourteenth to sixteenth week (7–13 cm. total fœtal length), and they found that at that time some of the fibres of the median longitudinal bundle are myelinated.

Collier and Buzzard (1903) reported that the ascending fibres "along the median anterior fissure are mostly fine fibres, although there are also some coarse fibres." One of the most important contributions to the

XUM

investigation of the size of the fibres of the ground bundles, as of all the fibres of the human spinal cord, was that of Häggqvist (1936). He studied the fibres in a transverse section of the third thoracic segment of the cord of a 13-year-old child. He found that throughout the white matter the most numerous fibres are those measuring less than 2 μ; he also found that there are many myelinated fibres measuring less than 1 μ; small fibres of less than 3 μ form the largest group of fibres in any part of, or tract in, the white matter. The zones which Häggqvist numbered 3 and 5 would contain a large proportion of fibres of the anterior ground bundle. About 45 per cent of the fibres of these zones measured 1 to 2 μ, and about 25 per cent 2 to 3 μ. Sie Pek Giok (1958) found that the descending fibres of the intermediate zone of the antero-lateral column measure 1 to 8 μ.

Other species.—An important study of the intrinsic fibres of the spinal cord of the young monkey was made by Tower, Bodian and Howe (1941) from whose paper our fig. 1 is taken. These investigators isolated a length of spinal cord by transecting it at two levels and cutting the posterior roots; these cords were "transected between the last thoracic and first lumbar segments and again below the sacral region." The cords were examined after sufficient time had passed for degeneration to take place in all the long descending fibres, and the posterior roots. Thus some of the fibres of their isolated segments are the ascending fibres of long tracts running to the encephalon, taking origin within the isolated segments; but the great majority of them are certainly the fibres of the fasciculi proprii. Their impression of their isolated segments was that "the number of fibres surviving is so great that loss of fibres is at first glance scarcely appreciated, until large myelinated fibres are sought. Healthy fibres are distributed everywhere throughout the white matter." But along the anterior surface of the anterior median fissure and along the anterior surface of the cord, they are sparse. The nearer the grey matter is approached, the denser the population of fibres of the ground bundle becomes. The fibres lying within the commissural tract were found to be large; and similar large fibres were found "adjacent to the grey matter between the bundles of emerging ventral root fibres."

Summary

Man.—The anterior ground bundle is present throughout the spinal cord; there are most fibres in this system in the cervical and lumbar enlargements. It consists of both ascending and descending fibres, though little is known what proportion of fibres belong to which category at the different levels of the cord or medulla oblongata. Certainly there are a large number of fibres ascending so as to connect the cord with the encephalon; such fibres run both within and without the median longitudinal fasciculus. Ascending fibres vary in length from those arising in

XUM

the caudal region of the cord and terminating in the tectum to fibres of less than one segment long; and descending fibres reach from the cervical region to the lumbar enlargement, while others are less than one segment long; there are descending fibres of every length between these extremes. Little is yet known of the proportion of the fibres of the various lengths, and of the manner in which the cells of one part of the cord are connected to those of another by means of the fibres of the anterior ground bundle. The shortest fibres are immediately around the grey matter, and the longer fibres are situated more peripherally. Most of the fibres of the bundle are fine, being less than 3 μ in diameter. The fibres run both ipsi- and contralaterally to their cells of origin. Immediately around the grey matter all the fibres running in a longitudinal direction belong to the ground bundle.

Our knowledge of the cells of origin of the fibres of this bundle is grossly insufficient. They are probably situated in the more medial and posterior parts of the anterior horn, in the substantia intermedia lateralis and possibly in the posterior horn.

The fibres of this bundle terminate not only where the main axon terminates, but also where their collaterals terminate. This aspect of the anatomy of the tract requires further investigation. The fibres thus terminate in the anterior horns throughout the spinal cord. Some fibres ascend into the encephalon, connecting the fibres arising in the cord with the motor cranial nerve nuclei. The fibres that have been described as running to the olive and to the reticular nuclei should be considered rather as spino-olivary and spino-reticular tracts.

The anterior ground bundle is the first tract of the spinal cord to myelinate. In the medulla oblongata, the first tract to myelinate is the median longitudinal bundle. It is probable that within the median longitudinal bundle the fibres which first show myelination are fibres ascending from the cord in the anterior ground bundle.

Other species.—When this knowledge is supplemented, as far as may be permitted, with the knowledge we have of species other than man, there is good evidence that there are enormous numbers of fasciculi proprii fibres scattered throughout the white matter of the cord, including the anterior ground bundles. There is some evidence that the cells of origin are to be found everywhere in the grey matter, though they are particularly collected in the substantia intermedia lateralis and in the anterior horn. All fibres, dendrites and collaterals that cross the mid-line, do so in the anterior commissure. Many of these fibres are collected together between the long descending tracts related to the anterior horn, the anterior horn, and the anterior commissure; here they are considered by some anatomists to constitute a tract—the commissural tract. Many of these fibres, in the monkey, are large. The fibres of this tract have divided axons, one branch ascending, the other descending; the two branches may be the same or

XUM

different in size. These fibres and their collaterals, of which there are very many, connect the commissural cells and the anterior radicular cells of the same and the opposite side.

The Lateral Ground Bundle

In this review, the lateral ground bundle will be considered to include the lateral limiting layer (seitliche Grenzschicht of Flechsig, couche limitante latérale, cornu-marginal zone) and the formatio reticularis (*see* fig. 2). The lateral limiting layer is divided into an anterior and posterior zone; the posterior zone is often called in the German literature the mediales Seitenstrangbündel. In Ramón y Cajal's terminology, the posterior part of the lateral limiting layer is called the système or the faisceau de la corne postérieure, the next more anterior part of the lateral limiting layer is called the système du noyau gris intermédiaire; and the part of the layer between the latter and the anterior roots is called the cordon intermédiaire. The formatio reticularis might be considered as a part of the white or a part of the grey matter. In the Nomina Anatomica, sponsored by the Congress of 1955, it is described as "lateral to the grey matter from which, in the lateral column, the cornu laterale projects. It consists of numerous small islets of grey matter intersected by white fibres, which run both vertically and horizontally." It is most marked in the more cranial cervical segments, but it is—as Rexed (1952) says—"a typical feature of the border of Lamina V on the lateral funiculus along the whole of the cord."

The lateral ground bundle (*see* fig 2), as we understand it, consists of all the intrinsic fibres of the white matter of that part of the cord situated between the most lateral of the anterior roots and the posterior roots.

Cells of Origin

Man.—Flechsig (1876) described fibres entering this bundle from the lateral part of the anterior horn. Von Lenhossék (1892) described the cells of origin as being in the intermediate region between anterior and posterior horns. The cells of the fibres occupying the most posterior part of the bundle were found to be situated more posteriorly in the posterior horn. Nearly all the cells were small and most of them were spindle shaped. Some of the cells were placed more medially abutting against the posterior column, the axons of such cells passing round the nucleus dorsalis to reach the lateral ground bundle.

Ziehen (1899) gives the following as the cells of origin of this bundle: cells of the lateral horn, cells of the anterior horn, the apical cells of the posterior horn (pericornual cells, pericornual magnocellular cell column of Jacobsohn and Papez, postero-marginal cells, Randzellen of Lenhossék, gruppi pericornuali del cordere laterale of Massazza, cellules terminales, marginales or limitantes of French authors, Marginalschichtzellen of

Marburg), and the cells of the nucleus proprius of the posterior horn. The relevant cells of the substantia intermedia lateralis are multipolar or spindle shaped and tend to lie in nests; their dendrites reach into the surrounding white matter. Most of their axons run ipsilaterally, but a few run contralaterally, crossing the mid-line in the anterior commissure. The axons arising from cells of the anterior horn mostly run in the anterior ground bundle, but a few run in this bundle. The fibres arising in the nucleus proprius of the posterior horn are few.

Von Lenhossék (1892) described some of the axons of this tract as dividing into two divisions; some of them have one division in the anterior column and one in the lateral column. Some neurones with cells of origin in the posterior horn divide into three, all three divisions remaining in the lateral ground bundle. Von Lenhossék found that there are more collaterals in the lateral than in the anterior ground bundle.

Other species.—The cells of the fibres of the lateral ground bundle are to be found at all levels of the cord. According to Ramón y Cajal (1899), in the chicken the great majority of the cells of the substantia gelatinosa send their axons into the lateral limiting layer: "almost all the fine axons which are to be seen in this layer are axons from the substance of Rolando." These axons are either bifurcated ones, dividing into an ascending and a descending branch, or they are single axons, one ascending, another descending. The apical cells of the posterior horn also give rise to the fibres of the lateral ground bundle; Ramón y Cajal describes these as large, fusiform, triangular or mitral-shaped. "Ces neurones sont en petit nombre; malgré cela, ils ne font jamais défaut ni chez les oiseaux ni chez les mammifères." They surround the posterior periphery of the substantia gelatinosa. Most of these axons run ipsilaterally, but some cross, in the posterior commissure, to the contralateral lateral limiting layer. The substantia intermedia lateralis and the grey matter at the anterior part of the base of the posterior horn, which Ramón y Cajal called the intermediate nucleus, contain cells giving rise to the axons of the most anterior part of the lateral limiting layer, the part just lateral to the emerging anterior roots; this fact was found by Ramón y Cajal to apply to the embryos, of the chicken, the rat and the cat. The fibres of the most anterior part of the lateral limiting layer, which Ramón y Cajal called the system of the intermediate nucleus, come mainly from the contralateral intermediate nucleus via the anterior commissure and also from the more posterior part of the ipsilateral intermedio-lateral nucleus. The fibres from the contralateral intermediate nucleus divide into ascending and descending divisions. Of other cells of these nuclei, the axons divide into two, the one branch running in the posterior part and the other in the anterior part of the lateral ground bundle. Other variations in the axon pattern are for one division to run in the lateral column and

XUM

the other in the posterior column, and for one division to remain on the side of the cell of origin, the other to cross to the opposite side. There are also cells in the posterior horn giving rise to axons, one division of which runs in the ipsilateral posterior column, the other running in the contralateral lateral column; the crossing is via the anterior commissure. Kölliker (1891*a*) also found the axons of the lateral bundle divided into two or three divisions.

Winkler (1918) stated: "On doit encore chercher l'origine de ces systèmes courts dans les cellules de la corne postérieure. Les ramifications des cellules zonales ou limitantes et des cellules terminales ou marginales de la substantia Rolando et les réseaux fibrillaires de la région des cellules de Gierke forment ensemble le grand territoire fibrillaire de la corne postérieure, d'où partent les systèmes que nous avons décrits comme voies ascendantes courtes dans le cordon latéral, le cordon antérieur et le cordon postérieur."

Bok (1928), who worked on the guinea-pig embryo, stated that the cells of origin of the fibres of the cornu-marginal zone are mainly in the contralateral nucleus proprius of the posterior horn. He found that the fibres that lie immediately lateral to the posterior horn arise in the intermediolateral nucleus. This confirms Ramón y Cajal's work.

Course

Man.—The lateral ground bundle is present throughout the spinal cord; its continuation into the conus was shown by Gierlich (1915). It is most developed in the cervical and lumbar enlargements. That part of the lateral ground bundle included in the formatio reticularis is particularly well developed in the cervical cord, fairly well developed in the lumbar cord, but poorly developed in the thoracic cord. The axons run both ipsi- and contralateral to their cells of origin, and are ascending and descending. The axons that cross do so in the anterior commissure. Many collaterals are given off by these axons, some leaving the axon early, before it reaches the white matter. The connexions these collaterals make have not been worked out in detail.

The length of these fibres, like those of the anterior ground bundle, varies between those starting at different levels of the cord and ending in the tectum (really spino-tectal fibres) to those of one segment length or less. Winkler (1918) found that there are in this bundle many fibres two or three segments long, particularly in the lateral limiting layer. Marie (1892) also concluded that the fibres of the lateral limiting layer are short; and Bechterev (1897) found the same. These conclusions were drawn from degeneration studies. Here, as in most tracts, the shorter fibres lie nearest to the grey matter.

From the work of Bechterev (1885, 1899), Hoche (1896*a*), Ziehen (1899),

Collier and Buzzard (1903), Bing (1905), Krumholz (1912), Winkler (1918), and Bok (1928), it is known that the lateral ground bundle contains both ascending and descending fibres. Bing found from his study of a case of poliomyelitis that most of the fibres are ascending, and that in the posterior part of the bundle in the sacral cord there are no fibres descending from the lumbar segments; but it should be realized that his conclusions are based on only one case. The ascending and descending fibres are intermingled throughout the tract.

The continuation of the lateral ground bundle into the medulla oblongata was studied by Bechterev (1885) in the human fœtus. He found that the fibres of the lateral ground bundle were less compactly arranged in the medulla than those of the anterior ground bundle. Bechterev, in 1897, published his findings on the part of the tract forming the lateral limiting layer. He found that this region of the cord contains "partly fibres of short course, partly fibres from the nucleus dorsalis (Clarke's column) and finally some fibres from the posterior roots"; the latter are passing through the lateral limiting layer, and those from the nucleus dorsalis are passing through on their way to make up the spino-cerebellar tract. He considered, on the basis of myelogenesis, that the lateral limiting layer should be divided into two regions—a posterior and an anterior. He found that the former extends from the lateral horn to the posterior horn "occupying some of the space between the pyramidial tract and the grey matter." He had reported these observations some years earlier, in the Russian edition of his Leitungsbahnen. Bruce (1896), who did not know this work of Bechterev's, found in a case of amyotrophic lateral sclerosis that the anterior part of the lateral limiting layer was degenerate, while the posterior part was intact. It is interesting to see that his subdivision of the lateral limiting layer into two parts was the same as that suggested by Bechterev from his myelogenetic studies. Krumholz (1912) also studied the lateral limiting layer. He found that these fibres are present throughout the length of the cord. In the lumbar region, the layer is broad and extends from the periphery of the cord to the posterior horn. Some of the fibres were found to ascend three to four segments, and some to descend the same distance; of such fibres there are more ascending than descending; he also found some thicker fibres, ascending and descending for seven segments in all.

Other Species.—There is good evidence on the course of these fibres in the dog and the cat; this has been provided by Sherrington and Laslett (1903), Tower (1937) and van Beusekom (1955). All of these workers provided excellent experimental evidence, and gave their results in adequate detail so that they can be evaluated by later workers. Sherrington and Laslett operated on 7 dogs and 2 cats; Tower operated on 3 six-week-old puppies by isolating segments and cutting posterior roots; and van Beusekom carried out on cats 11 hemicordotomies, 4 complete divisions

XUM

of the cord, and 2 mid-line myelotomies; in 5 cats two hemicordotomies, both on the same side of the cord, were performed.

Tower showed in the lumbar and sacral region of the dog that there are many intrinsic fibres adjacent to the grey matter in the posterior part of the lateral column and also many at the surface, with fewer fibres in the region in between. Those fibres concentrated on the surface, at least in the upper lumbar cord, are likely to be spino-cerebellar. This concentration of fibres near the grey matter was found also by van Beusekom in the fifth lumbar segment of the cat; he showed that many of these fibres are descending. He found in the thoracic region a concentration of ascending and descending fasciculi proprii "just lateral to the intermediate horn. It might be possible that these fibres, which are mainly of small calibre, connect sympathetic central nuclei of different segments with each other." Van Beusekom emphasizes the fact that intrinsic fibres are scattered among the fibres of "all well-known long systems. . . . The thin propriospinal fibres occurred even in areas of rather compact fibre tracts, such as the lateral pyramidal tract."

With regard to the length of the fibres of this bundle, Sherrington and Laslett found in the cat and dog that within the lateral column there are both long and short descending intrinsic fibres; in fact there are more fibres of this type in this region than in the anterior or posterior columns. Some of the longest fibres were found to reach from the seventh cervical segment to the caudal region of the cord. All these fibres are ipsilateral. Van Beusekom found in the cat that many of the fibres of the lateral and anterior ground bundles surrounding the grey matter do not extend farther than one segment cranially from their cells of origin; peripheral to such fibres are fibres extending for two or three segments.

Terminations

Man.—The fibres terminate throughout the length of the cord; a large proportion of them continue out of the cord into the medulla oblongata. These were studied particularly by Bechterev (1885) in the human fœtus. He found that most of the fibres run into the reticular formation. The majority run into the medial part, that is the region medial to the hypoglossal nerve, and most of them run to the nucleus centralis. A very few go to the lateral part of the reticular formation, to its most medial region. He traced these fibres to reticular nuclei at the level of the middle of the pons; a few were found to continue to the nucleus centralis superioris; some were found to run to the superior olive; these fibres came from the more posterior region of the lateral ground bundle. In a later study Bechterev (1899) found that these fibres send collaterals to the motor nuclei of the fifth, seventh, ninth, and twelfth cranial nerves. The fibres within the lateral part of the reticular formation ascend further cranially, terminating in the reticular formation at about the middle of the pons. A

XUM

very few ascend farther and terminate in the nucleus centralis superioris. Some of the fibres of the more posterior parts of the lateral ground bundle run to the olive. All such fibres are best considered as spino-reticular and spino-olivary.

With regard to the fibres of the lateral ground bundle within the spinal cord, von Lenhossék (1892) showed that they terminate between the anterior and posterior horns, in the "middle zone of the grey substance." According to Bechterev (1899), fibres of the anterior part of the lateral limiting layer run to cells of the anterior horn, whereas those of the posterior part run to cells of the posterior horn.

The collaterals of the fibres of the lateral ground bundle, according to von Lenhossék (1892), terminate in the anterior horn, the substantia intermedia lateralis and the lateral part of the posterior horn, as far posteriorly as the anterior limit of the substantia gelatinosa; they are fewest in the substantia intermedia lateralis. According to Kölliker (1891*a*), the collaterals of these fibres that cross in the anterior commissure run to the anterior horn, though possibly some also run to the posterior horn.

Other species.—Ramón y Cajal found many collaterals in this tract, particularly in the posterior part of the lateral limiting layer. These run to the substantia intermedia lateralis.

Intermingling of Tracts

Man.—The fibres of this bundle are intermingled with the other tracts of the lateral column.

Myelination Number, and Size of Fibres

Man.—That part of the cord near the grey matter where the majority of the fibres of this bundle run was found to myelinate at two different periods, by Flechsig (1876). He found in his youngest fœtus—a five-month-old one measuring 25 cm. total length—that the "vordere gemischte Seitenstrangzone" was already myelinated; this is equivalent to all the white matter between the most lateral of the anterior roots and the anterior limits of the lateral corticospinal tract, except a rather wide region occupied by the anterior part of the spino-cerebellar tract. He found that the lateral limiting layer—situated between the posterior horn and the lateral corticospinal tract—myelinates about the sixth month (32 cm.) fœtus. Bechterev (1885) confirmed Flechsig's findings regarding the myelination in the 25 cm. long fœtus. Ziehen (1899) found myelination proceeding in the "vordere gemischte Seitenstrangzone" in the five to seven-months-old or 25 to 35 cm. long fœtus; he found that the lateral limiting layer myelinates in the sixth month or 32 cm. long fœtus. This was confirmed by Hösel (1900). Keene and Hewer (1931) found that "the lateral ground bundle begins to myelinate about twenty-two to twenty-four weeks." The fibres of the bundle that surround the grey matter myelinate before the more peripherally situated fibres; and the

XUM

anterior fibres myelinate before the lateral. The formatio reticularis is strongly myelinated by the eighth month (47 cm. fœtus) according to Barbé (1938). We have found no other references to myelination of this part of the cord.

With regard to the size of the fibres, Flechsig (1876) classified the fibres of the lateral limiting layer as fine and very fine. In Häggqvist's (1936) measurements of the fibres of the third thoracic segment of a 13-year-old girl, the lateral limiting layer corresponds to his areas 9 and 6. His area 9, which lies lateral to the posterior horn, contained the largest proportion of finest fibres of any part of the lateral and anterior columns of the cord; 67 per cent of the fibres in this area measured less than 2 μ. The region which was the next richest in these smallest fibres was his area 7, where there would be many lateral ground bundle fibres; here these smallest fibres formed 62 per cent of all fibres. In area 6, the more anterior part of the lateral limiting layer, they formed 55 per cent of all fibres.

Other species.—Bok (1928) stated that the fibres of the cornu-marginal zone myelinate before all other systems of the spinal cord.

The great number of fibres in the lateral ground bundle in the monkey has been shown by Tower, Bodian and Howe (1941). In the lumbar segments the distribution of these fibres was dense right through from the grey matter to the surface of the cord (although most dense near the grey matter) but in the sacral segments they were sparse beneath the surface of the lateral and the antero-lateral parts of the cord. Only the lumbar and sacral segments of the cord have been investigated in the manner of Tower, Bodian and Howe; other methods of investigation are not so informative with regard to the fasciculi proprii.

With regard to the size of the fibres, Tower (1937) showed in her study of the intrinsic fibres of the lumbosacral region of the dog that the great majority of intrinsic fibres measure 1 μ or less, "but axis cylinders up to 7 μ were found. . . . Fibres remaining in the posterior half of the white matter are all exceedingly small, 1 μ more or less, and largely unmyelinated." In the anterior half of the cord, fibres of 2 μ or more occurred, and some fibres measured 5 μ. "The greater number lie in the reticular zone adjacent to the grey matter, while a few are scattered through the most medial part of the anterior column." In the monkey, Tower, Bodian and Howe found in the formatio reticularis and in the lateral limiting layer fibres of all sizes, "ranging from a fineness almost too minute to be measured to fibres nearly as large as any to be found in the intact cord. . . . Diameters ranged from 0·5 μ to 15 μ for the poorly defined outside sheaths, and from 0·5 μ to 6 μ for axis cylinders. The largest fibres are, of course, unmistakably myelinated." They found many large fibres in the lumbar segments. These large fibres of the lateral ground bundle are grouped "in the reticular formation adjacent to the

dorsolateral border of the anterior horn and extending around its dorsolateral tip." Van Beusekom (1955) found in the cat that in the cornumarginal zone there are 19 per cent of fibres of less than 1·5 μ, 45 per cent of fibres of 1·5 to 3 μ, 25 per cent of fibres of 3·5 μ, and 8 per cent of fibres of 5 to 10 μ.

SUMMARY

Man.—The lateral ground bundle includes all the fasciculi proprii in the white matter between the posterior roots and the most lateral of the anterior roots; it does not include Lissauer's tract. The fibres lying closest to the grey matter are often called the lateral limiting layer; here the fasciculi proprii fibres are concentrated. The lateral ground bundle is present throughout the cord, and is most developed in the cervical and lumbar enlargements. It consists of both ascending and descending fibres; our knowledge is inadequate on what proportion of fibres belong to each category at the various levels of the cord and the medulla oblongata. The axons of this bundle branch, and they run both ipsi- and contralaterally to their cells of origin, although most are ipsilateral. The fibres vary in length from those arising in the cord and terminating in the tectum to fibres of less than one segment long. In the lateral limiting layer the fibres are short, though the longest may be seven segments long. The lateral limiting layer consists of two parts, an anterior with the cells of origin located more anteriorly, and a posterior part with the cells of origin located more posteriorly. The fibres of the lateral limiting layer are described as fine and very fine. The axons of this tract give off many collaterals.

The cells of origin of the lateral ground bundle are situated in the substantia intermedia lateralis and in the posterior horn; here they are next to the posterior column, among the apical cells, and in the cells of the nucleus proprius; some are also in the anterior horn.

In the medulla oblongata the axons run to various reticular nuclei and to the olive, and they send collaterals to the cranial motor nerve nuclei. In the cord they terminate in the substantia intermedia lateralis, in the anterior and in the posterior horn. They terminate throughout the length of the cord.

Most of the bundle is myelinated in the five-month-old or 25 cm. fœtus; but the part between the posterior horn and the lateral corticospinal tract myelinates in the six-month-old or 32 cm. fœtus.

The part of the ground bundle which abuts against the posterior horn contains more fine fibres than any other region of the anterior and lateral columns of the cord.

Other species.—When this knowledge is supplemented with the more ample knowledge we have of species other than man, it is known that there are vast numbers of such fibres in the monkey. The majority of them are

XUM

small, but in the formatio reticularis of the lumbar region (only this region and the sacral region have been investigated) there are also many large fibres.

The cells of origin are known to be more widely distributed than has so far been found in man. In the chicken, the majority of the cells of the substantia gelatinosa send their axons into the lateral limiting layer. This layer also contains the axons of cells taking origin near the apex of the posterior horn and all around the substantia gelatinosa. Further anteriorly in the posterior horn, the cells situated at its base and the cells of the substantia intermedia lateralis also give rise to fibres of the lateral limiting layer. These have all been found in birds, cats and rats. It is also probable that the nucleus proprius of the posterior horn gives origin to some of the contralateral fibres.

In the cat, there is evidence that there is a collection of ascending and descending fibres of this system immediately lateral to the substantia intermedia lateralis. In the dog many of the fibres near the grey matter in the lumbar region are descending; and in the cervical region there are long descending fibres running to the caudal region of the cord; these are ipsilateral.

The Posterior Ground Bundle

The term posterior ground bundle has been more misused than the terms anterior and lateral ground bundle; Flechsig used the term to mean the fasciculus cuneatus; the term is used by most workers to mean the cornu-commissural tract; others use it to mean the fasciculi proprii scattered throughout the posterior columns.

We will not use the term to include all the fasciculi proprii of the posterior columns, for in these columns there are other organized tracts of such fibres, studied, named, and traditionally considered as entities. Nageotte (1903) classified the fasciculi proprii of the posterior columns as large fibres grouped in tracts—for instance, the septo-marginal tract—and as fine fibres—those fibres scattered throughout the entire area of the posterior columns. Such a classification is logical; but it has not been generally accepted. It therefore seems best to us to use the term posterior ground bundle to designate the fine fibres of the fasciculi proprii scattered throughout the whole area of the posterior columns (*see* fig. 2).

Although this review concerns our knowledge of the anatomy of the intrinsic fibres of the cord, it is impossible to proceed without mentioning some features of the anatomy of the posterior root fibres in the posterior column. All, or almost all the posterior root fibres that enter the posterior column bifurcate into an ascending and a descending division, according to Ramón y Cajal. Excellent pictures of the bifurcation and of the collaterals of these posterior root fibres are given in his textbook; Their further course will not be followed in this section. It is important

to realize, however, that entering posterior root fibres have descending divisions as well as ascending, and according to Rasdolsky (1928), who did excellent work on the posterior root of the dog, there are as many collaterals of the descending divisions as there are of the ascending divisions, but they do not extend as far.

It will be recalled from the introduction of this review that a lesion at any one level will cause degeneration only in the parts of the fibres cut off from the cells of origin; and so, supposing there is a lesion of the posterior columns at the first thoracic segment, degeneration caudal to the lesion will be shown up only in those descending fibres of the cervical roots that descend into segments caudal to the lesion. Although that is well known, much of the controversy on the shape and the position of the region of degeneration following lesions affecting the posterior columns was really unnecessary; for it was concerned with making comparisons between degeneration caudal to lesions situated at different levels. Much of this controversy, which occurred in the later years of the nineteenth and the earlier years of the twentieth centuries, was concerning the origin of the different fibres situated within the posterior columns. It was not agreed whether the various named tracts were made up of intrinsic or extrinsic fibres or of both. Although this controversy has largely been forgotten, it has not been settled. When we now examine the evidence presented, we need to keep in mind the fact that after total transverse lesions of the cord, or what the older workers called transverse myelitis, fibres of both origins, intrinsic and extrinsic, will degenerate; only after lesions restricted to roots or to the grey matter may conclusions be drawn on the intrinsic or extrinsic origin. Besides, in pathological or traumatic conditions causing total division of the cord, there is bound to be accompanying damage to the posterior roots and often to their ganglia too. This has been realized by some workers, but not by all.

The descending divisions of the posterior roots are both fewer and thinner than the ascending divisions; and so, when the Weigert-Pal technique is used, such thin degenerating fibres may not be found. Here again positive staining is to be accorded preference in judging of the presence of such fibres.

Cases of tabes dorsalis have been made use of by many workers in the controversy concerning the intrinsic or extrinsic origin of fibres in the posterior columns. It is argued that as the pathological process of tabes affects only fibres of extrinsic origin, fibres that are degenerate are posterior root fibres and fibres that are intact have an intrinsic origin. Yet others consider that too little is known of the pathological process of tabes to permit such generalizations; they are willing to believe that syphilis may affect also the intrinsic fibres of the cord and their cells of origin. Nowadays most pathologists agree that the degenerative changes affecting the posterior columns in tabes are secondary to the pathological process

XUM

affecting the posterior root fibres outside the cord; and so it may be legitimate to make use of cases of tabes to provide evidence that the fibres affected by this disorder are posterior root fibres and that those unaffected are indeed intrinsic fibres. It is, however, obvious that as the pathological process of tabes affects the roots to various degrees, not all the fibres are likely to show degeneration. Thus cases of tabes can show where descending posterior root fibres are situated when these fibres are degenerate; but when the fibres are normal histologically, then no conclusions may be drawn regarding their origin.

Another group of cases which is useful in throwing light on the extrinsic or intrinsic origin of fibres consists of cases in which the lesion is restricted to the grey matter. Unfortunately (from an anatomical point of view) such cases are rare, or they are rarely reported.

Before reviewing the evidence concerning the fasciculi proprii of the posterior columns, it is convenient to give the views of Bok (1928, 1951, 1957) on the subject. Bok considers that there are no myelinated intrinsic fibres within the posterior columns. For, he states, that when many cases of posterior root lesions are collected together, it becomes clear that every part of the posterior columns contains posterior root fibres. With regard to the unmyelinated fibres, he regards it as proved that there are such fibres in the posterior roots, but as unproved that there are such fibres originating anywhere else. To quote his words (1957) regarding the existence of fibres other than posterior root fibres in the posterior columns —"Not proved, not likely, but not excluded."

Cells of Origin

Man.—Kölliker and van Gehuchten were unable to find the cells of origin of these fibres in the posterior horns. Von Lenhossék (1892) stated that they existed, though they are few in all mammals; he wrote that most of them are situated near the white matter of the posterior columns, and a few are in the lateral part of the posterior horn near the substantia gelatinosa. Lenhossék described the cells of origin as small cells of a type intermediate between Golgi I and II; they have one dendrite larger than the others, and this penetrates the posterior column. Von Lenhossék emphasized that as there are so few of these cells in the posterior horn, there can be only a few fibres of a fasciculus proprius in the posterior columns. Nageotte (1904) found these fibres taking origin in the medial basal nucleus of the posterior horn and in the substantia gelatinosa.

Other species.—With regard to division of these axons, von Lenhossék (1892) found that, in the guinea-pig and in the rabbit, these axons were either single or they divided into two; in the latter case, one division might continue in the posterior column and the other run in the lateral column.

Course

Man.—Nageotte (1903, 1904) described the fine intrinsic fibres, not

confined to definite bundles, as running transversely and longitudinally. "On peut supposer que ces fibres sortent horizontalement de la substance grise pour se courber ou se bifurquer lorsqu'elles sont arrivées dans les cordons." Nageotte's description of these fibres is of their spreading out from the medial border of the posterior horn in a fanwise manner, so that they are scattered regularly throughout the whole posterior column. On account of this fanwise distribution they are seen on transverse section to be most compact near the stratum spongiosum and least compact near the periphery. Some of them traverse the median septum. Ramón y Cajal showed that these fibres are both ascending and descending; and they are short fibres. They are probably present throughout the cord; Nageotte found them in the fasciculus cuneatus in the cervical cord.

Terminations

Man.—It is probable that the fibres run to the grey matter of the medial part of the posterior horns. It is unknown where those seen running towards the septum on transverse sections terminate.

Fibres of the ground bundle of the posterior columns apparently do not ascend into the medulla oblongata.

Intermingling of Tracts

Man.—These fibres clearly must intermingle with all the other fibres of the posterior columns. Ramón y Cajal showed that they are scattered among posterior root fibres.

Myelination, Number and Size of Fibres

Man.—The fibres described by Nageotte are unmyelinated. They measure 0·5 to 2 μ; Nageotte found most of them are less than 0·5 μ. There are also larger fibres of intrinsic origin in the posterior columns.

Other species.—In the monkey, "the dorsolateral region of the posterior column where the medial division of the posterior root debouches into the cord" was the region of the cord where Tower, Bodian and Howe found fewest fibres of the fasciculi proprii. The size of these fibres "averaged around 1 μ, but with a scattering of larger fibres."

Lissauer's Tract

Lissauer's tract is bounded anteriorly by the network of fibres of the substantia gelatinosa and posteriorly by the subpial neuroglia and the entering posterior root.

Before it was realized that this small region of the cord contained a tract, it received many names. Flechsig (1876) first described it as the lateral part of the posterior radicular zone; Kölliker (1893) also classified it as part of the posterior columns; Bechterev (1886) called it the posterior root zone of the lateral columns; Trepinski (1898) labelled it as his fifth system. It used to be known as the Randzone to German workers, as

XUM

the zone marginale to French workers; it has also been called the zona terminalis, and the hintere Markbrücke, as it joins the posterior and lateral columns together over the posterior horn.

As long as parts of the body are named after those who described them, this tract with justice will be named after Lissauer; for his description (1885, 1886) of the fibres of this system is excellent. He pointed out that fine fibres separate themselves from the rest of the entering posterior root and enter the cord slightly lateral to the rest of the root fibres. It did not occur to Lissauer, however, that some of the fibres he was describing might belong to the intrinsic fibres of the cord; he thought they were all posterior root fibres. It was Nageotte (1904) who first came to the conclusion that the fibres described by Lissauer are intrinsic fibres. He reached this conclusion from studying cases of lesions of all the roots of the cauda equina, stained by the Marchi, Weigert-Pap, and Nissl techniques. His evidence justified him in stating that the majority of the fibres of the tract are of intrinsic origin, but it did not prove that this was true of all. Indeed, he had previously (1895) published a case of tabes, with marked diminution in the number of fibres in Lissauer's zone; and he had attributed this to degeneration and disappearance of posterior root fibres. His later manner of viewing Lissauer's tract was to consider it as that part of the zone that contains the intrinsic fibres. Gierlich (1915) considered that the zone described by Lissauer contains mostly intrinsic fibres; his view as founded on a case was one in which the lesion was restricted to the grey matter of the conus. Laignel-Lavastine (1908), who studied a case of meningo-vascular syphilis affecting the roots of the cauda equina, by means of the Marchi and the Weigert-Pal techniques, concluded that the fibres are intrinsic; he regarded it as still possible that posterior roots might make some contribution to the tract. Ramón y Cajal (1899) carried out his usual excellent study in the chicken, noting that the fibres were mixed with posterior root fibres. Leslényi (1912) wrote a classical paper on this tract, studying it in a great number of species; he showed that the fibres running longitudinally are nearly all of intrinsic origin. All workers now agree that the tract consists largely of intrinsic fibres. The tract is usually divided into lateral and medial parts, the two being separated by the incoming posterior root fibres; the medial part is much smaller than the lateral. Ranson (1913, 1914*a* and *b*), who studied this tract in man, in the rhesus monkey, the cat, rabbit, squirrel, guinea-pig, and rat, found that the majority of the fibres situated lateral to the posterior root are of intrinsic origin, whereas about half those medial to the root are intrinsic. Tower (1937) presented some beautiful photographs of her silver preparations of the lumbosacral segments of puppies, in which she had carried out two transverse sections and divided the posterior roots. She found many intrinsic fibres within Lissauer's tract. In 1941, she carried out

the same procedure in the monkey with Bodian and Howe. They found that the densest concentration of intrinsic fibres can be found "lateral and medial to the tip of the posterior horn"; this is the region of Lissauer's tract. Earle (1952) found in the cat that posterior root fibres contribute only to the medial division of the tract, the lateral division being made up entirely of intrinsic fibres. In all, he reckoned that three-quarters of the fibres of the tract are of intrinsic origin and a quarter are extrinsic.

Bechterev (1886) devoted a paper to this region of the cord, studying it in the human fœtus. But at that time it was not realized that most of the fibres were of intrinsic origin. Bechterev pointed out that Lissauer's zone is related in size to the size of the substantia gelatinosa; it is smallest in the thoracic region, largest in the upper cervical cord. It is present throughout the cord.

Cells of Origin of Intrinsic Fibres

Man.—Ranson (1914*b*) studied these fibres in four normal humans; he found that the fibres originate in the substantia gelatinosa.

Other species.—Golgi (1880, 1903) described the typical cells of origin in the substantia gelatinosa and in the posterior horn immediately adjacent to the substantia gelatinosa; the species was not mentioned. Ramón y Cajal (1899) described the cells of origin in more detail in the chicken and the dog. In the substantia gelatinosa, the cells are elongated "dans le sens vertical" (cranio-caudally), as can be clearly seen from his fig. 150. Their processes also run cranio-caudally. In young embryos Ramón y Cajal found that some of the axons divide; both branches might then run in Lissauer's tract, or the one branch might run in Lissauer's tract and the other in the lateral limiting layer. Earle (1952), from his study of this region in the cat, concluded that in addition to the cells of the substantia gelatinosa, the apical cells and the cells of the nucleus proprius of the posterior horn give origin to the fibres of this tract.

Course of Intrinsic Fibres

Man.—Lissauer (1886) described fine fibres as running in all directions in this tract; he emphasized that many run longitudinally, and that these are ascending fibres. Ziehen (1899) found after transverse cord lesions that the fibres degenerate both cranially and caudally to the lesion.

Ranson (1914*b*) described the intrinsic fibres as originating in the substantia gelatinosa, passing transversely through the stratum zonale, and then running in a longitudinal direction before returning to the substantia gelatinosa.

With regard to the length of the fibres, Collier and Buzzard (1903) found that they never could "trace the very fine fibres of Lissauer's zone for more than a segment or two above a degenerated posterior root." This provides evidence that the fibres are short.

XUM

Other species.—Ramón y Cajal (1899), from Golgi, silver, and methylene blue preparations, found that the intrinsic fibres of this tract bifurcate into an ascending and a descending branch. According to Ranson (1913, 1914*a*), the fibres leave the substantia gelatinosa and run horizontally through the stratum zonale; they then turn vertically in Lissauer's tract. Earle (1952) found that they are short fibres "of not more than one or two segments in cranio-caudal extent." He found no long fibres in the tract, neither of intrinsic nor of extrinsic origin. According to Earle, the fibres consist of "the processes of marginal cells, substantia gelatinosa cells, and cells of the posterior grey columns. Thus, the lateral part of Lissauer's tract seems to correspond to the numerous intersegmental fibres which surround the grey matter of the spinal cord elsewhere."

Terminations of Intrinsic Fibres

Man.—The fibres of this zone were found by Lissauer (1886) and by Bechterev (1886) to terminate in the substantia gelatinosa. According to Ranson (1914*a*), they traverse the zonal layer to reach the spongy layer of the substantia gelatinosa.

Intermingling of Tracts

Man.—Ranson (1914*a*) found that the lateral part of the tract consists entirely of intrinsic fibres. Of the medial part, the fine fibres are mixed intrinsic and extrinsic; the unmyelinated posterior root fibres "form a large part, perhaps the major part" of the medial part of the tract. The myelinated fibres are of intrinsic origin; no myelinated fibres of the posterior root enter Lissauer's tract. The fibres of the tract are separated by the entering posterior roots, as has been explained above.

Myelination, Size and Number of Fibres

Man.—All anatomists are in agreement that this is one of the last tracts to myelinate; most have found that it begins to myelinate in the eighth or ninth fœtal month. Flechsig (1876, 1890) noted that Lissauer's zone (the lateral part of the posterior root zone in his terminology) is the last region of the posterior columns to myelinate. Bechterev (1886) gives the earliest date of all investigators; he found myelination proceeding in the sixth to seventh month (33 cm. fœtus). Trepinski (1898) found the fibres myelinating in the eighth to ninth month (42 cm. fœtus); in Trepinski's scheme of myelination, these fibres form the fifth system. Ziehen (1899) stated that the fibres myelinate "towards the end of fœtal life"; and Winkler (1918) found that they myelinate immediately after birth; Kaufman (1921) found that they myelinate in the eighth fœtal month; and Lucas Keene and Hewer (1931) found that they begin to myelinate at the ninth fœtal month.

Lissauer described these fibres as fine. Ziehen (1899) stated that they

XUM

measure 2 to 3 μ at the most. Nageotte (1904) described them as being mostly less than 0·5 μ. Ranson (1914*a*) found that this tract "is composed of closely packed, fine axons, the majority of which are non-myelinated." The exact fibre spectrum and the number of fibres has not been worked out in man.

Other species.—The proportion of myelinated to unmyelinated fibres and the origin of the two kinds of fibres was worked out by Ranson (1913, 1914*a* and *b*). He found that the majority of the myelinated fibres of Lissauer's zone are intrinsic; "in the lateral half of Lissauer's tract (in the sixth lumbar segment of the cat) practically all of the medullated fibres are endogenous, while in the medial half a large number, perhaps 50 per cent, are endogenous." Tower (1937) found in the lumbar and sacral regions of the puppy that most of the intrinsic fibres measure about 1 μ; and Tower, Bodian, and Howe (1941) found in the monkey that the tract is "composed of the most minute fibres, most of them well under 1 mμ."

SUMMARY

Man.—Lissauer's tract is present throughout the cord; it is most developed in the upper cervical region, and least developed in the thoracic cord. The majority of fibres that compose this tract are intrinsic; all those of the lateral part and most of those of the medial part are intrinsic. The tract contains both ascending and descending fibres, and they both extend for one to two segments from their cells of origin. Both the cells of origin and the cells around which the fibres terminate are cells of the substantia gelatinosa; and so it is seen that the tract consists of fine, closely packed, short fibres which connect longitudinally the cells of the substantia gelatinosa. Whether there are other cells of origin is unknown. The tract is divided by the entering posterior root fibres into a medial and a lateral part. This tract is one of the last tracts of the spinal cord to myelinate.

Other species. As in species other than man it is likely that there are also cells of origin among the apical cells and in the nucleus proprius of the posterior horn, it remains to be found out whether this is also so for man. In the cat, in the lumbar segments, almost all of the myelinated fibres of the lateral part of the tract are of intrinsic origin, whereas half of those of the medial part are intrinsic; and as the lateral part of the tract is larger than the medial, it will be realized that the myelinated fibres are mostly intrinsic. However, in the puppy and the monkey most of the fibres measure 1 μ or less. As the size of the fibres and the presence or absence of myelination is related to the size of the species, the knowledge of species other than man tells us nothing of the fibre spectrum in man.

THE CORNU-COMMISSURAL TRACT

The cornu-commissural tract is situated along the anterior two-thirds

of the posterior horns, in the cornu-commissural region, and posterior to the posterior commissure. It is illustrated in the lumbar segments in fig. 3.

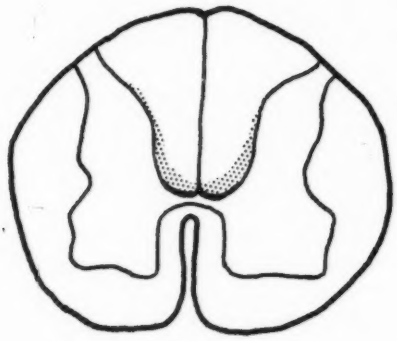

FIG. 3.—Diagram to show the location of the cornu-commissural tract in the lumbar segments.

The term "cornu-commissural tract" will be used here to mean the fibres of the region called by Flechsig (1876, 1890) the ventral or anterior root zone and by Marie (1892) the cornu-commissural zone. The zone was called the Marginalzone by Westphal; this is an unfortunate choice of name, for the marginal zone or Randzone is more commonly used to designate the zone occupied by Lissauer's tract. In much of the earlier German literature this region is called the ventrales Hinterstrangsfeld; this, however, is not quite the same as the cornu-commissural zone, for the cornu-commissural tract occupies only the anterior part of the area to which the name has been given. Many workers look upon this tract as the ground bundle of the posterior columns; reasons for not using this term in this way have already been given.

Almost all workers are agreed that this tract consists of fibres both of the fasciculi proprii and of the posterior roots, the larger proportion being the former. Most of the tract remains clearly stained in advanced cases of tabes dorsalis and subacute combined degeneration, where the posterior roots are affected. It is often involved in anterior poliomyelitis and, according to Nageotte and Riche (1907), in amyotrophic lateral sclerosis. With traumatic lesions of the roots degeneration is slight in the cornu-commissural tract. Tower, Bodian, and Howe (1941) found in their monkeys that this is one of the regions of the cord which contains the densest concentration of fasciculi proprii fibres.

Cells of Origin of Intrinsic Fibres

Man.—Bruce (1897) and Dejerine and Thomas (1902) found the cells

of origin of fibres of this tract at the base of the posterior horn. Van Gehuchten (1906) gives the posterior horn and the substantia gelatinosa as the locations of the cells of origin. The evidence on which these statements were based was not presented. Rexed (1952) found that the cells of his Lamina I, cells covering the most peripheral part of the "dorsal cell column," send their axons "to the adjacent parts of the dorsal funiculus."

Other species.—Ramón y Cajal (1899) found the cells of origin in the newborn kitten in the nucleus cornu-commissuralis (the internal basilar nucleus of Ramón y Cajal) of the lumbar region and in the substantia gelatinosa.

Course

Man.—The tract lies against the posterior commissure; it fills the cornu-commissural angle, and lies along the anterior two-thirds of the posterior horns. It is most developed in the lumbar cord, and within this region, at the fourth and fifth segments; here it is seen on transverse sections to occupy the anterior quarter of the posterior columns. Cranial to the lumbar cord the part of the tract lying along the posterior commissure is very narrow antero-posteriorly. It was shown by Russell (1898*b*) that the tract is still present in the cervical cord; this can be seen clearly in transverse sections of the cord in cases of tabes; it was shown by Bruce (1897) and by Bechterev (1925) that it is still present in the tip of the conus. The form of the tract on transverse section is different at the different levels. Caudal to the first sacral segment, the medial part is prolonged posteriorly along the septum so that it becomes joined to the septo-marginal tract; and so, at this level, there is a continuous tract between the periphery of the cord and the posterior commissure. Cranial to the first sacral segment, the two tracts become separated by the incoming ascending posterior root fibres. The fibres of the tract, according to Bruce, are "almost exclusively" ipsilateral. Ziehen (1899) agrees with this, and states that the fibres which do cross to the other side do so in the grey commissure.

It is difficult to determine from the published work the direction of conduction of these fibres. The posterior root fibres within the tract are certainly both ascending and descending. Of the intrinsic fibres, it has been stated that they degenerate in an ascending direction, and also that they do so in a descending direction. Redlich (1897), Ramón y Cajal (1899), and Bruce (1900) found fibres degenerating in an ascending direction, and Müller (1897, 1899) and Ramón y Cajal (1899) found them degenerating in a descending direction. Gierlich (1915) from one case of a lesion restricted to the conus found that the intrinsic fibres are mostly ascending; but at this level they could hardly be otherwise.

The individual fibres are short. Müller (1897) found that fibres

XUM

transected at the third lumbar segment had all disappeared into the grey matter by the fifth lumbar and first sacral segments.

The sacral posterior root fibres that contribute to this tract all lie, according to Wallenberg (1898), near the median septum. Nageotte and Riche (1907) discussing the lumbar region write that the posterior root fibres "lie along the head of the posterior horn"; they consider that the most anterior fibres of the cornu-commissural tract are the intrinsic fibres; for these are the fibres that remain after lesions of the cauda equina and in cases of tabes. In three cases of poliomyelitis reported by Batten and Holmes (1913), in which the lesions were restricted to the grey matter, the degeneration was mainly in the angle formed by the posterior horn and the posterior commissure. Thus all these investigators agree that intrinsic fibres occupy this angle.

Terminations

Man.—It is to be presumed that these fibres enter the grey matter lying immediately adjacent, that is the grey matter of the posterior horns and posterior commissure.

Other species.—Münzer and Wiener (1899, 1910) found in the pigeon, the rabbit, and the dog, that most of the fibres are short; but there are some long fibres of intrinsic origin that run to the cuneate and gracile nuclei. Rothmann (1899) found the same in the dog; he found that most of the few long ascending fibres run to the gracile nucleus.

Intermingling of Tracts

Man.—The fibres of the tract are a mixture of intrinsic and posterior root fibres, though the posterior root fibres tend to occupy the more medial part of the cornu-commissural zone. Sosa (1945*a* and *b*) has shown that the part of the tract that lies along the posterior commissure contains collaterals of neurones situated posterior to the central canal in the posterior white commissure; he calls these septal collaterals.

Myelination, Size and Number of Fibres

Man.—Flechsig (1876, 1890) found myelination in his material starting in this zone between the fifth and sixth months (24 cm. fœtus) in the lumbar region, which was the region which he investigated in most detail. Trepinski (1898) confirmed this, and added that it occurs at the same time in the thoracic and cervical regions. Kaufman (1921) did not find that this anterior zone myelinates before the rest of the posterior columns, for she found the whole of the anterior and middle zone myelinating simultaneously. She did not find that the rigid schematization of the myelination of the posterior columns implied by Flechsig and by Trepinski gives a true idea of the facts. Bechterev (1925) found that it myelinates at the same time as the oval field. Keene and Hewer (1931) found myelination beginning in the cornu-commissural zone at the 26th

to the 28th week. On going through the accounts of those who described myelination in the posterior columns, it seems to us that those who reported their findings tended to forget that this part of the cord contains fibres of various origins and that they were not dealing with a single tract.

Nageotte (1903) found that the cornu-commissural tract consists of large fibres. Häggqvist (1936), using his own stain, found otherwise. In the upper thoracic cord of the 13-year-old girl which he investigated his area 12 corresponds to that part of the cornu-commissural tract which lies along the commissure. In this region 55 per cent of the fibres are less than 2 μ diameter, and only 2 to 3 per cent measure more than 7 μ.

Other species.—Ramón y Cajal found a great many fine fibres "in the region bordering on the medial boundary of the substance of Rolando and in the deep or ventral portion of the posterior column, that part known under the name of the cornu-commissural zone of Marie."

Tower (1937) found in the remaining segments between two transections in dogs that this is the region of the posterior columns where intrinsic fibres are most concentrated. When she repeated this work on the monkey with Bodian and Howe (1941), she was able to confirm this for that animal; this region and Lissauer's tract are the most rich in intrinsic fibres. Nearly all these fibres were found to be "small and seemingly unmyelinated"; a few large myelinated fibres were also found "deep, adjacent to the posterior commissure."

SUMMARY

Man.—The cornu-commissural tract is present throughout the cord and is most developed in the lower lumbar region. It lies against the medial aspects of the posterior horns and along the posterior commissure; and it thus surrounds the grey matter in the same way as the more internal fibres of the lateral and anterior ground bundles do in the lateral and anterior columns. It consists mainly of ipsilaterally running fasciculi proprii. There is some evidence that the cells of origin of the intrinsic fibres are in the posterior horn, near the tract; but the evidence for this is inadequate. The few posterior root fibres running within the course of the tract and the intrinsic fibres are both ascending and descending fibres. The intrinsic fibres would seem to connect the regions of subjacent grey matter to similar areas at other levels. Although the fibres of the tract are short, our knowledge of the kind of chain these fibres form at the various levels is most inadequate. The evidence on myelination in this tract is discrepant. It is apparently the earliest part, or one of the earliest parts, of the posterior columns to show myelination.

Other species.—In the monkey the great majority of these fibres are small and probably unmyelinated; there are a few large myelinated fibres very near the grey matter—as in the case of the lateral and the anterior ground bundles.

XUM

The Comma Tract

The comma tract is a name which has been universally accepted; the only synonyms known to us are the fasciculus interfascicularis, and the Zwischenzone. Schultze described these descending fibres and named them the comma tract in 1883. They had previously been illustrated in a paper by Westphal (1880). Schultze traced the tract about 2·5 cm. caudal to the lesion, which, in his case, was at the level of the fourth and fifth cervical segments. Illustrated in fig. 4 is the classical conception of

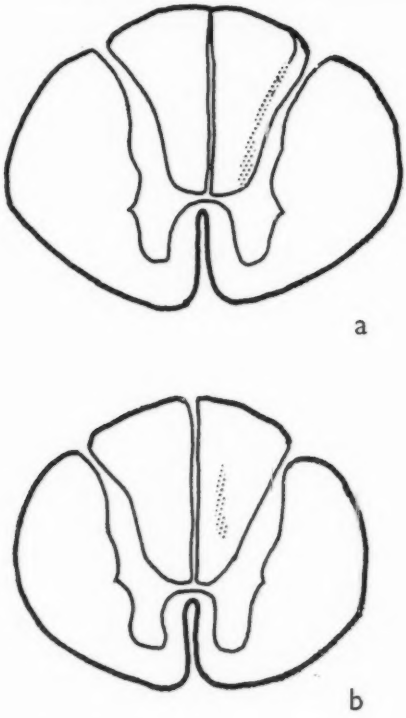

Fig. 4.—Diagram to show the classical conception of the comma tract as derived from degeneration studies.

The degeneration is shown about two segments (fig. 4*a*) and six segments (fig 4*b*) caudal to a lesion of one or two upper thoracic posterior roots.

degeneration in the comma tract caudal to a lesion of one or two roots in the upper thoracic region.

The comma tract is not found to occupy the same position in all cases. The reason for this has been stated by van Gehuchten (1906): "Il n'existe pas *un* faisceau en virgule, mais un grand nombre de faisceaux en virgule

superposés les uns aux autres." Further, the form on transverse section and the position of the comma within the posterior column vary according to the level of the lesion causing the degeneration and to the segment examined. The definite comma shape is found only with degeneration of cervical roots and in the segments just caudal to the lesion; when these degenerating fibres are traced further caudally, only the head of the comma remains. (The comma is an inverted comma.) Most workers believe that the tract is present in the lower cervical segments and throughout the thoracic cord, although van Gehuchten states that one finds the typical comma after lesions anywhere in the thoracic or lumbar cord. Whether the comma tract exists as such at all levels caudal to the cervical segments has been maintained by some and denied by others. And finally, whether the tract consists of the descending division of posterior root fibres or of intrinsic cord fibres has never been decided.

Before considering the last question—whether we are dealing here with intrinsic or extrinsic fibres—we must mention some features of the anatomy of the descending divisions of the posterior root fibres. When a posterior root is cut, descending degenerating fibres are seen scattered ipsilaterally throughout the posterior column; there is maximal degeneration in the postero-lateral region, adjacent to the substantia gelatinosa. As this degeneration is followed caudally, it becomes narrowed from side to side, and becomes curved, taking on the form of a comma in transverse section. Ramón y Cajal's (1899) description of the descending branch of posterior roots is as follows. "In the cervical region the descending branch is situated in the lateral third of the fasciculus of Burdach; in the upper thoracic region, it is probably localized in the middle third of this fasciculus . . . in a curved shape; finally, in the lower thoracic and lumbar portions of the medulla, it gradually passes medially until it comes, perhaps, to lie against the mid-line. In a word, it seems probable to us that the descending branch behaves like the ascending, that is to say it occupies in the posterior column a position as lateral as the sensory root from which it is derived is situated cranially. It is equally probable that there are long and short descending paths and that the number of the latter is not the same at all segmental levels of the medulla. For these reasons, the extent and the form of the patch of descending degeneration varies from case to case. It seems probable to us that the cervical medulla gives rise to many long descending fibres, of which possibly some reach the lumbar cord, while the lumbar medulla is rich in short descending and long ascending branches."

Opinions regarding the intrinsic or extrinsic origin of the fibres of the comma tract are summarized in Table I. In considering this evidence, one should remember that the absence of the fibres in Weigert-Pal stained material constitutes no sort of evidence; for this is a narrow tract and its fibres are intermingled with the other fibres of the posterior columns.

XUM

TABLE I. OPINIONS ON ORIGIN OF FIBRES OF COMMA TRACT

Authors	*Date*	*Intrinsic*	*Extrinsic*
Schultze	1883	−	+
Tooth	1889	probably +	−
Marie	1892	probably +	−
Daxenberger	1893	+	−
Gombault and Philippe	1894	+	−
Dejerine and Sottas	1895	−	+
Dufour	1896	+	−
Hoche	1896	+	−
Flatau	1897	−	+
Schaffer	1898	−	+
Zappert	1898	−	+
Jacobsohn	1899		+
Dejerine and Theoari	1899	+	mainly +
Nageotte and Ettlinger	1899	+	−
Schaffer	1899	+	+
Ziehen	1899	+	+
Bruce	1900	+	+
Homén	1901	−	+
Dejerine and Thomas	1902	+	+
Collier and Buzzard	1903		+
Batten and Holmes	1913	−	+
Winkler	1918	−	+
Bok	1928	+	+
Gagel	1932		+

As has been said above, views based on transverse lesions of the cord have to be discountenanced, for such lesions shed no light on the source of the fibres; this has not always been realized by those who reported such cases. For this reason the material reported on by Schultze, Tooth, Dufour, and Hoche is of no value in this controversy. The opinions of the workers mentioned in this paragraph cannot be held to contribute adequate evidence, for various reasons. Marie (1892, 1894), and also Daxenberger, stated that this tract is not involved in tabes, and tabes being a disorder affecting only the posterior roots, they considered that the fibres of the comma tract must belong to an intrinsic cord system. Marie (1894) considered that this view was supported by these fibres being involved in pellagra, a disorder which he regarded as essentially affecting the grey matter; however, Nageotte has given adequate reasons for considering pellagra as not being a disorder of the grey matter but as a disorder affecting mainly the roots; and so such cases do not provide the evidence favouring Marie's view. Gombault and Philippe (1894) examined some cases with lesions of the posterior roots; they found no degeneration of the comma tract. It is apparent that they did not have much material to support this view, and what they did have was stained only by the Weigert-Pal technique; at the time they worked few other cases of lesions restricted to the roots had been reported. Later (1895)

they admitted that with the Golgi technique posterior roots can be seen to divide into ascending and descending divisions. Hence, little weight should be given to their inability to find possible descending divisions in material stained by the Weigert-Pal method. Flatau stated that his view of the extrinsic origin of these fibres was based mainly on Marchi preparations of posterior root lesions; yet he presented as his main material a case of myelitis. Zappert reported 2 cases, 1 of compression of the cord and 1 of a few-days-old child with inflammation of the pia mater involving particularly the nerve roots of the cervical region; in both cases the comma tract was degenerate. His view could be criticized, as he presented no photographs or drawings; and opponents of his view could legitimately object that the posterior columns themselves would probably also be involved in the pathological processes he described. Although Dejerine and Theoari stated that their views were based on many cases of posterior root lesions, the 2 cases they presented were of Pott's disease and of a softening of the cord respectively. Nageotte and Ettlinger's views were based on 2 cases of "transverse myelitis" and 6 cases of tabes. Bruce presented his evidence at a conference in Paris; and so no photographs, records or diagrams remain. He stated "Les fibres exogènes descendantes des régions cervico-dorsales occupent la position du faisceau en virgule de Schultze dans une partie de leur trajet." The opinions of Dejerine and Thomas and of Bok were given in textbooks; no evidence supporting their views, apart from their large experience, was presented.

The following workers produced good evidence on which to assess the source of the fibres of the comma tract: Schaffer (1898*a*), Russell (1898*a*), Jacobsohn (1899), Homén (1901), Collier and Buzzard (1903), Orr (1906), Batten and Holmes (1913), Winkler (1918), and Gagel (1932). Degeneration of the comma tract following lesions restricted to posterior roots was reported by Schaffer, Jacobsohn, Dejerine and Theoari, Homén, Collier and Buzzard, Winkler, and Gagel. Such evidence establishes, in our opinion, that many (if not all) of the fibres of the tract have an extrinsic origin and are in fact the descending divisions of posterior root fibres. Dejerine and his colleagues believed that the tract is made up of both intrinsic and extrinsic fibres, for they found that when a lesion involves only the posterior roots, the degeneration in the comma tract extends only a little distance caudally, but when it involves the whole cord, the degeneration extends further caudally. This argument does not seem to be very good, as a lesion involving the cord must involve more descending divisions of posterior roots than one restricted to some roots outside the cord. Winkler, however, did not agree with the facts. He stated that there are a number of cases in which no degeneration is found in the comma tract in the presence of posterior root lesions. Apart from the observations of Marie, Daxenberger, and Nageotte and Ettlinger, that the tract is not involved in cases tabes, there is Gombault and Philippe's

XUM

failure to find it degenerate in cases of posterior root lesions, which have already been mentioned. Schaffer in two papers in 1898 brought forward evidence that the comma tract consists of extrinsic fibres. He found it degenerate in a case of pachymeningitis cervicalis affecting the roots and in a case with a lesion of the seventh cervical root and in cases of tabes; in both of his main cases only Weigert-Pal staining was used. He even pointed out that as transverse lesions of the cord involve also the posterior roots "if only intramedullarily," such cases do not provide evidence of the intrinsic origin of these fibres. However, in a further paper published in 1899 he changed his view and gave it as his opinion that the comma tract is mixed, and mainly of intrinsic origin. The further evidence that he brought forward consisted of a case of compression of the cord, the fifth lumbar roots being also affected, and a good case in which there was degeneration of all the posterior roots of the caudal extremity of the cord, stained both by the Marchi and Weigert-Pal techniques. In addition, he showed a cat in which the lumbar and sacral roots were degenerate. Yet as this material supported the view that the fibres of this tract are extrinsic, one cannot understand why Schaffer was led to change his mind. Nevertheless he wrote in 1899 that he had previously been too much under the influence of Schultze, and that he now thought the fibres were mainly intrinsic.

Orr brought forward evidence to show that the comma tract consists of intrinsic fibres. In his case there were multiple tumours compressing the posterior roots in the thoracic region; and the comma tract was not found to be degenerate. But his case was complicated; for "in the lower dorsal region there was a small tumour of the posterior columns growing inwards from the cord margin, and in addition there were several myelitic foci on either side of the median septum." Hence this case hardly brings evidence that the fibres are of intrinsic origin, as there were multiple lesions; and if the case shows anything with regard to this tract, it would suggest that it does not exist. There is another paper which was not listed in Table I, as the author was not concerned with the origin of any fibres: the paper on the relationship of some forms of combined degeneration of the cord to one another and to anæmia by Russell. In the cases reported of subacute combined degeneration the extrinsic fibres are degenerate; the excellent photographs of transverse sections of the cord show only intrinsic fibres intact. As no comma tract can be seen, this constitutes evidence that the fibres of the tract are of extrinsic origin.

Good evidence obtained from lesions of the grey matter was reported by Batten and Holmes; they examined 3 cases of poliomyelitis; from this material they concluded that the fibres in question are extrinsic. Winkler also concluded that the tract contains only the descending limbs of posterior root fibres; for he always found it degenerate when the

posterior roots were involved in a lesion and never when there was a lesion of the grey matter, as in poliomyelitis and syringomyelia. Gagel reported a case in which there had been surgical division of the posterior roots from the fourth cervical to the fourth thoracic segments. Degeneration could be traced "in long collaterals by means of the Marchi method down into the sacral region of the cord."

SUMMARY

It is likely that the comma tract consists of extrinsic fibres, namely of the descending divisions of the cervical and upper seven thoracic posterior roots. The location of the descending divisions of the lower thoracic, lumbar and sacral roots is not as definite as that of these more cranial roots; they are apparently more scattered, and their location is less constant at different levels. Evidence that the comma tract consists also of intrinsic fibres is not good. Apart from the criticisms given above, no one has shown degeneration in the tract with lesions of the grey matter. The fact that this is not so much a tract as a collection of descending posterior root fibres accounts for the region of degeneration being seen in different positions in various cases: the position of the degenerating fibres is related to the segmental level of the lesion and to the distance caudal to the lesion at which the tract is looked for. Most workers consider that lesions of roots caudal to the seventh thoracic segment cause no degeneration in the comma tract; for the fibres constituting this tract are the descending divisions of the roots of the fasciculus cuneatus.

The next matter to consider is this: with which (if any) fibre systems of the posterior columns is the comma tract continuous; in other words, do the fibres of the comma tract at one level continue into the other recognized fibre systems at more caudal levels, such as the oval field or septo-marginal tract?

To be prepared to answer this question, the lesion must be located sufficiently caudally, it must involve several roots, and the material must be appropriately stained. It is clear that as the descending divisions of the cervical posterior roots do not extend into the lumbar cord, a lesion of these roots will not cause descending degeneration sufficiently caudally to involve the septo-marginal tract or oval field; and, from cases with the lesion in the cervical region, conclusions may not be drawn with regard to the descending divisions of posterior root fibres of the thoracic region. Obvious though this is, such conclusions have been reached by some workers who have written on this subject.

Gombault and Philippe, Dejerine and Theoari, Stewart (1901), and Gagel stated that the comma tract continues into the septo-marginal tract and the oval field. Gombault and Philippe presented no evidence; their

XUM

view was a hypothesis. Dejerine and Theoari found the comma tract still present at the fourth lumbar segment following mid-thoracic lesions. Their first case is most convincing; for following a lesion at the fourth thoracic segment, there was descending degeneration as far as the fourth sacral segment; the degenerating fibres were first in the comma tract; at the tenth thoracic segment they were in the septo-marginal tract, and at the second lumbar segment they were in the oval field. In Stewart's case, the descending degeneration was seen to run into the oval field and continue within the rest of the septo-marginal tract. Gagel's case is important, as the lesion was a pure one, consisting of surgical division of posterior roots, and as death supervened 29 days after the operation, at a time suitable for Marchi staining. Gagel states: "the fibres lie in the comma tract of Schultze and further caudally in the oval field, and finally they pass towards the periphery of the cord."

Hoche (1896*b*), Ziehen, Bumke (1905) deny that this tract continues into the septo-marginal tract. In Hoche's second case, the lesion was at the seventh thoracic segment; the degeneration could be traced to the third lumbar segment. This may not have been caudal enough to judge whether this terminal degeneration was in the oval field or not. In Hoche's first case the lesion was at the eighth cervical segment, and so there was no question of the descending degeneration occurring caudally enough to give evidence on the question. Ziehen states that he never saw the tract degenerating caudal to the eleventh thoracic segment; but as this conclusion was based on cervical and upper thoracic lesions, it is irrelevant to the question of the position of the descending divisions of posterior roots of the lower thoracic segments. And further, such negative evidence has no weight when other reliable observers have seen such degeneration descending well into the lumbar cord. In Bumke's case, degeneration in the comma tract started at the fifth and sixth cervical segments and descended for ten segments; and so his view that there is no connexion between this tract and the septo-marginal tract is valueless.

SUMMARY

The descending divisions of the posterior roots that lie at first in the comma tract may remain in the comma tract or they may lie in the septo-marginal tract, particularly in that part of it known as the oval field.

Cells of Origin

Man.—The cells of origin of the comma tract are the ganglion cells of the posterior root ganglia.

Terminations

Man.—The descending divisions of the fifth and sixth cervical roots have been traced as far as the twelfth thoracic segment; those of the eighth cervical roots have been traced to the twelfth thoracic segment;

those of the fourth thoracic roots have been traced into the sacral cord; and those of the seventh thoracic root have been traced as far as the fourth lumbar segment.

Most workers traced these descending fibres into the grey matter of the posterior horns and the region of the posterior commissure.

Myelination, Size and Number of Fibres

Man.—It is unknown when these descending fibres myelinate.

Although the size and the number of the fibres of the cuneate fasciculus is adequately known, it remains unknown what proportion and which of these fibres are descending.

The Septo-marginal Tract

The classical conception of the septo-marginal tract is illustrated in fig. 5; it is shown in the lower thoracic, the lumbar, and the sacral regions of the cord. The tract is situated along the posterior periphery of the cord; at the first and second lumbar segments, it fits its name by extending along the periphery of the cord and along the median septum, filling in the angle between these two features; at the third, fourth and fifth lumbar segments it forms the oval field, which abuts at some points against the posterior commissure; at the first sacral segment it again reaches the periphery of the cord; at about the third sacral segment, the two tracts of each side meet along the septum, forming a triangle on transverse section, the apex of which points anteriorly; this is the triangle of Gombault and Philippe.

The tract differs from the comma tract in that the comma tract is made up only of descending divisions of posterior roots, whereas the septo-marginal tract consists of both posterior root fibres and intrinsic fibres.

This tract was first described by Hoche (1896*a* and *b*), and by Bruce and Muir (1896) who proposed the name. The earlier anatomists found three regions of the posterior columns particularly rich in fasciculi proprii: the oval field of Flechsig, the tract of Hoche, and the triangle of Gombault and Philippe. In 1894 Gombault and Philippe put forward the view that the triangle they had described was a continuation caudally of the oval field. It seems likely that the three tracts are essentially one. Whether the fibres that form the comma tract also continue into this tract has been discussed already. There is some confusion in the literature on this tract, for there is a minority of workers who do not agree that these three components form one tract; and there is also much inconsistency in the naming of the different groups of fibres. With regard to synonyms, the oval field is also known as the oval area of Flechsig, the oval centre, the zone médiane or bandelettes médianes, or (in Italian literature) the fascette lentiforme. The septo-marginal tract is also called the bundle, bandelette or peripheral field of Hoche, and the dorsomedial bundle. Some workers use the term dorsomedial sacral bundle or faisceau postéro-medial to

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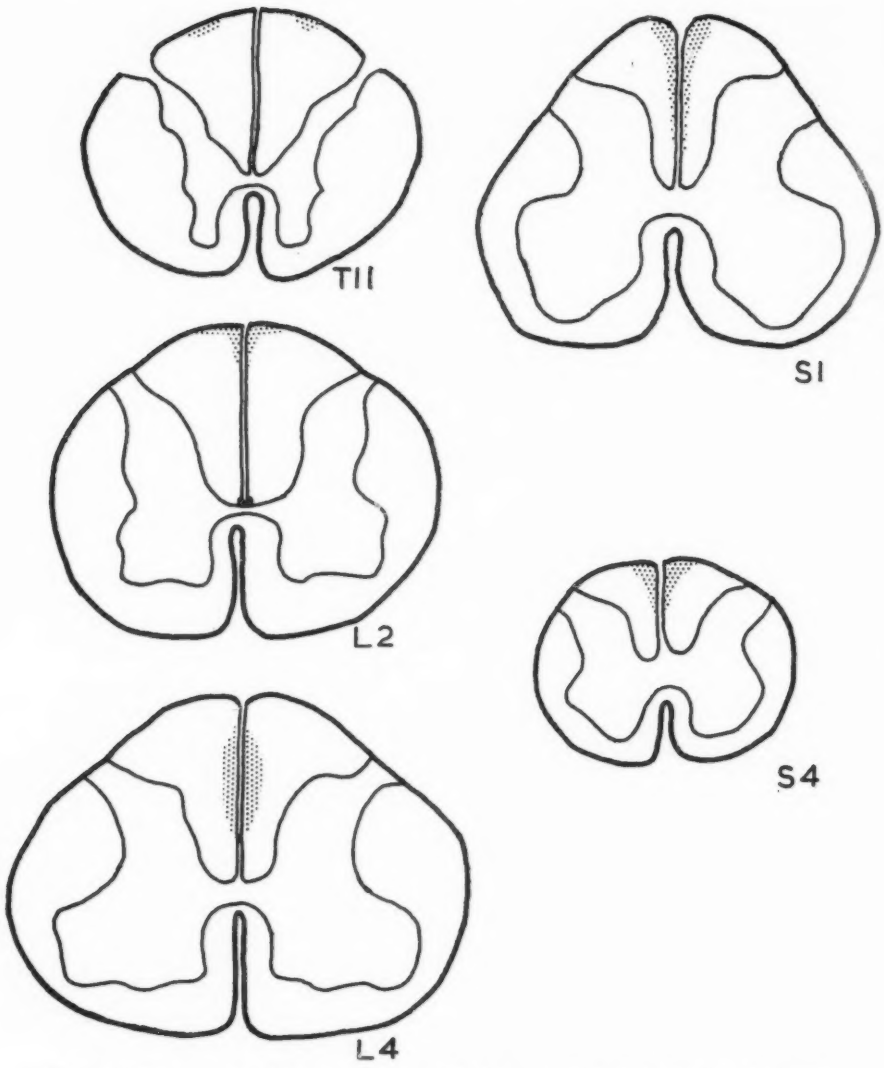

FIG. 5.—Diagram to show the location of the septo-marginal tract in the lower thoracic and lumbo-sacral cord.

describe the more caudal parts of this tract, while others use it as a synonym for the triangle of Gombault and Philippe.

The conclusions of those workers who had evidence on which to judge

of the extrinsic or intrinsic origin of the fibres of this tract are presented in Table II. An attempt to evaluate this evidence will now be made. It

TABLE II. OPINIONS ON ORIGIN OF FIBRES OF SEPTO-MARGINAL TRACT

Authors	*Date*	*Intrinsic*	*Extrinsic*
Gombault and Philippe	1894	+	
Souques and Marinesco	1894	+	+
Dejerine and Sottas	1895	+	
Dejerine and Spiller	1895	+	+
Bruce and Muir	1896	+	
Dufour	1896	+	
Hoche	1896	+	−
Bruce	1897	+	
Redlich	1897	−	+
Russell	1898	+	+
Schaffer	1898		Almost entirely +
Wallenberg	1898	mostly +	+
Dejerine and Theoari	1899	+	+
Nageotte and Ettlinger	1899	+	+
Müller	1899	+	
Schaffer	1899	+	−
Ziehen	1899	+	+
Dejerine and Thomas	1902	+	+
Collier and Buzzard	1903	possibly	+
Nageotte	1903	+	+
Orr	1906	mostly +	+
Laignel-Lavastine	1908	+	−
Batten and Holmes	1913	−	+
Gierlich	1915	mostly +	+
Winkler	1918		+
Bok	1928	+	+
Gagel	1932		+

will be seen from the table that most workers consider that this is a mixed tract, containing both intrinsic and extrinsic fibres.

As has been said already, cases of transverse lesions of the cord contribute no evidence on the origin of the fibres, for such lesions involve roots as well as fasciculi proprii. The opinion of Bruce and Muir seems to have been based on a case of fracture-dislocation causing a complete crush of the cord; Hoche presented 2 cases of total transverse lesions; and 2 of the cases reported by Wallenberg were of transverse lesions. The opinions of Ziehen, Dejerine and Thomas, and Bok are given in textbooks; no evidence in their support was given.

Cases of tabes dorsalis in the literature have been used by different workers to provide evidence in favour of both the intrinsic and the extrinsic origin of the fibres of this tract. Gombault and Philippe stated that their triangle is not involved in tabes; they therefore concluded that it is composed of intrinsic fibres. They found further evidence in support of this view in the fact that in cases with lesions involving the posterior

XUM

roots, their triangle is not usually involved. As only few cases with lesions restricted to the posterior roots had been recorded at the time they were writing, they made their suggestions only tentatively. Bruce (1897) also found that the septo-marginal tract is not involved in tabes; yet in his short paper presented in Paris, reported in 1900, he stated that the tract contains fibres of both origins; why he considered there were extrinsic fibres in the tract cannot now be known. Redlich, who studied many cases of tabes, found the tract degenerated in this disorder, and therefore he concluded that this tract is made up of the descending divisions of posterior root fibres. Schaffer (1898*a* and *b*) similarly quoted cases of tabes as evidence that most if not all of the fibres of the triangle of Gombault and Philippe are of extrinsic origin. Yet by 1899 his views had changed, and he had come to the conclusion that the fibres are intrinsic. He based his new opinion on 3 cases: a case of compression of the cord involving also the fifth lumbar roots; a case without a diagnosis with degeneration of all the posterior roots of the caudal extremity of the cord; and a case of a cat with degeneration of the sacral roots. Of this material, the first case cannot be allowed as evidence, for such a lesion involves fibres of both origins, the cat is irrelevant as we are concerned with man, and so the second human case alone constitutes good evidence. Schaffer's evidence then consists of a human case of lesions of posterior roots demonstrating that the descending divisions of these roots do not run in this tract, and of many cases of tabes demonstrating that they do. Nageotte and Ettlinger concluded that the tract contains fibres of both origins; their views were based on 6 cases of tabes and 2 cases of transverse lesions of the cord. However, Nageotte and Riche (1907) considered that the oval field does not form a part of the tract constituted by the septo-marginal tract and the triangle of Gombault and Philippe: as the oval field is not involved in tabes, at least not in the early cases, they considered that these fibres must be of intrinsic origin. Winkler based his view on his experience of tabes. He considered that the "faisceau postéromedial (the more caudal part of the septo-marginal tract) est constitué, sinon exclusivement du moins presqu'entièrement, de fibres radiculaires postérieures descendantes des segments thoracicques inférieurs et des segments lombaires supérieurs."

The following workers presented evidence that the septo-marginal tract is made of the descending divisions of posterior root fibres, or both these fibres and intrinsic fibres. Souques and Marinesco found in a case of a cyst involving the lumbar and sacral roots that there was degeneration in the oval field and in the cornu-commissural zone; they therefore concluded that these areas contain extrinsic fibres; they accepted Gombault and Philippe's evidence that the tract has many intrinsic fibres. The case reported by Dejerine and Spiller, one of compression of all the roots of the cauda equina, showed marked degeneration in the

triangle of Gombault and Philippe; they concluded: "la grande majorité des fibres du triangle de Gombault and Philippe sont en connexion directe avec les racines postérieures"; and they further concluded that the oval area contains largely intrinsic fibres, as it showed no degeneration in their case. Wallenberg reported a case of a tumour of the sacrum involving the roots caudal to the fourth lumbar, including the third lumbar root on one side. He concluded that most of the fibres of the tract are certainly of intrinsic origin, while some are the descending divisions of posterior roots of the thoracic, lumbar, and upper sacral segments. Russell (1898*a*) published his usual excellent contribution to the subject, illustrated by very good photographs. He reported 4 cases, 1 with degeneration of the first sacral roots, another with a tumour involving the seventh cervical root and the lateral part of the cord, a third with an intramedullary tumour of the lower part of the lumbo-sacral cord involving the whole conus, and a fourth of a complete transverse cord lesion. He found the fibres of the first sacral root entering the septo-marginal tract, and he also found that the tract contains intrinsic fibres. Collier and Buzzard stated—and their words are still true today—"Cases of a single extramedullary root lesion which can be examined by the Marchi method, and which are not complicated by other intramedullary degenerations, are of some rarity." They reported two such cases of lesions of the posterior roots. They found that lumbar and sacral root fibres are present in large numbers in the septo-marginal tract, both in "the sacral triangle and the region of the oval area." In their first case the degenerated posterior root fibres "eventually became bunched in the septo-marginal angle, forming one-half of the well-known triangle." Orr reported 2 cases, the second of which is useful in determining the origin of these fibres; this case showed multiple tumours involving the thoracic roots. "There was very slight degeneration in the septo-marginal tract." He concluded that these fibres are of both extrinsic and intrinsic origin.

The following cases constitute evidence that this tract contains a large proportion of intrinsic fibres. Dejerine and Sottas reported a case of crush fracture involving only the cauda equina. In this case the septo-marginal tract was free from degeneration. They then came to the conclusion that the fibres of the region are intrinsic cord fibres; for, as they said: "Il est très important de signaler que l'étendue de ces zones saines augmentaient à mesure que l'on se rapprochait de la terminaison de la moelle, car cette circonstance prouve que les fibres saines n'étaient pas des rameaux descendants venus des fibres radiculaires saines sus-jacentes, mais bien des fibres d'origine medullaire." Dufour reported a case of a tumour involving the cauda equina; he also concluded from this case that the septo-marginal tract is made up of intrinsic fibres. Russell (1898*b*) in his paper on subacute combined degeneration of the

XUM

cord showed evidence in photographs indicating the degeneration of all long tracts, the intrinsic fibres remaining intact; from this paper it may be concluded that at least a large proportion of the fibres of the tract are of intrinsic origin. Müller studied the origin of the fibres of the sacral region of the cord in many cases. He found that the further caudal a transverse lesion is, the more degeneration there is in the septo-marginal tract. He felt it was unjustified to come to a definite conclusion but inclined to the view that the fibres are of intrinsic origin. Laignel-Lavastine reported a case of syphilitic meningo-radiculitis affecting the whole cauda equina; he found no degeneration in the oval field or the triangle of Gombault and Philippe, and so he concluded that the fibres are of intrinsic origin.

Cases in which the lesions are restricted to the grey matter are few; and those who have studied them have usually paid attention to questions of pathological interest and have not realized the importance of such material to the subject of anatomy. Batten and Holmes studied 3 cases of poliomyelitis with proper regard to anatomical problems. All 3 cases had the destruction in the lumbar segments, in 2 it was also present in the cervical enlargement and in the thoracic segments. They found no degeneration in the septo-marginal tract; and so they concluded: "We must therefore accept the conclusion that the system of descending fibres contained in Schultze's comma, Hoche's bundle, Flechsig's oval area, and Gombault and Philippe's triangle are wholly exogenous or root origin." It seems justified to suppose that had their cases had the lesions in the sacral region, they might have come to other conclusions. Gierlich published an important case. A jockey fell off his horse while riding in the typical flexed and crouched-up position and landed on his buttocks. This fall caused a lesion restricted to the grey matter of the cord, extending from the second sacral segment caudally; the roots were unaffected. As the septo-marginal tract failed to stain in Weigert-Pal preparations, while the posterior root fibres stained normally, Gierlich concluded that the fibres of this tract are of intrinsic origin.

From all this evidence it is to be concluded that this may be a mixed tract made up of both posterior root and intrinsic cord fibres; the evidence with respect to the intrinsic fibres is inconclusive.

Cells of Origin

Man.—The cells of origin of the intrinsic fibres are within the posterior horn. Wallenberg (1898) considered that the cells are posterior and lateral to the central canal. Massazza (1924) considered that the cells are in the medial part of the posterior horn, and that they are all small cells.

The cells of origin of the extrinsic fibres are neurones of the posterior root ganglia.

XUM

Course

Man.—The course of the tract is most easily seen with lesions of the posterior roots. Any intrinsic fibres of the tract accompany these extrinsic fibres. The extrinsic contribution to the septo-marginal tract would seem to consist of the following posterior root descending fibres: those from the thoracic roots, which may reach to the oval area; those from the lumbar roots, which reach into the oval area and may reach into the triangle of Gombault and Philippe; and those from the sacral roots, which run in the triangle of Gombault and Philippe. It is possible that also descending divisions of lower cervical roots may sometimes descend as far as the oval area. In the cases from which this matter can be judged it is obvious that the amount of degeneration depends on the severity and extent of the pathological process involving the roots. In 2 cases of transverse cord lesions in the thoracic region reported by Dejerine and Theoari (1899) and in the case reported by Gagel (1932) of surgical division of the posterior roots of the lower cervical and upper thoracic segments, there was degeneration throughout all the components of the septo-marginal tract, including the triangle of Gombault and Philippe.

There is no doubt that degeneration in this tract occurs in a caudal direction; and so it may be concluded that all the fibres are descending. But there are some ascending fibres in the triangle of Gombault and Philippe. The more caudal the region, the greater the proportion of ascending fibres.

According to Bing (1905), some of the fibres cross in the grey commissure; yet this cannot be so for the fibres of the triangle of Gombault and Philippe, as in the conus there is no grey commissure.

Terminations

Man.—Most workers have found that the fibres of this tract terminate by passing forwards through the fibres of the cornu-commissural zone to enter the grey matter at the base of the posterior horn. Here, according to Müller (1899), they end in the neighbourhood of the large multipolar cells of the substantia intermedia lateralis. According to Bruce (1897) and to Müller they terminate in the lower sacral and the coccygeal segments. The fibres of the oval field terminate further cranially than those of the triangle of Gombault and Philippe.

The descending divisions of the posterior root fibres in this tract run to the ipsilateral posterior horns.

Myelination, Size and Number of Fibres

Man.—Trepinski (1898) found that at the sixth month (28 cm. fœtus) there is no region of the posterior columns completely free from myelination. Kaufman (1921) showed that at eighth to ninth month (44 cm. fœtus) the posterior columns are completely myelinated. She

XUM

found that on the whole myelination starts earlier in the antero-medial region of the posterior columns that in the posterior parts. And she found that the intrinsic fibres myelinate early.

There seems to be no evidence on the number and the size of these fibres.

Anterior Septal Fibres

Hoche (1896*a* and *b*) described in his 2 cases of compression of the cord, in addition to the septo-marginal tract and the comma tract, a few mid-line fibres adjacent to the septum, which descended for one segment. These fibres could not be confused with the fibres of the oval field, as the lesions were at the eighth cervical and the seventh thoracic segments respectively, and as the oval field exists only in the lower lumbar segments. The existence of such fibres was confirmed by Collier and Buzzard (1903). They found them "lying in single file along the ventral third of the septum, not reaching the grey matter and not extending more than one or two segments clear of the lesion. They are moderately large fibres. They pass ventrally along the septum towards the grey matter" and enter it in the septo-marginal angle. Bumke (1905) also found these fibres for two segments caudal to the compression of the cord at the fifth and sixth cervical segments in his case.

The White Commissures

The anterior and posterior commissures will be considered here; the grey commissure will be considered in the section devoted to the intrinsic fibres of the grey matter. The general anatomy of these commissures is well known. However, mention should be made that in the conus there is no posterior commissure and no grey commissure, whereas the anterior commissure is well developed.

The commissures are made up of fibres, collaterals, and dendrites of long descending and ascending tracts. These will not be mentioned further here; what is known about the descending tracts in man already has been reviewed by us (1955), and what is known about ascending tracts will be considered in later papers. Here, only the fibres of the intrinsic system of the cord that cross in the white commissures will be mentioned.

The Anterior Commissure

The anterior commissure is well developed throughout the cord. It transmits nearly all the fibres of the anterior and lateral ground bundles that cross the cord. Kölliker (1891*b*) found in his embryological material that many of the fibres crossing in the commissure are collaterals of the fibres of the anterior and lateral columns; some of these axons divide within the commissure.

Ziehen (1899) found that myelination starts at the end of the fifth fœtal month (25 cm. fœtus). But Keene and Hewer (1931) found fine

myelination present in the anterior commissure at the 14th week; this is at the same time as some of the fibres of the median longitudinal bundle and the anterior ground bundle show myelination.

Sosa and Andrew (1947) described in the human lumbo-sacral cord "a fasciculus of tangential, arciform nerve fibres, lying on the surface of the white matter"; many of these fibres cross from the opposite anteromedian part of the anterior horn in the anterior commissure and run in the anterolateral zone of the border of the cord. They named these fibres the superficial circumflex fasciculus of the cord. The fibres are not myelinated. This work needs to be confirmed.

The Posterior Commissure

According to Ramón y Cajal, there are posterior commissural cells, but they are rare. He found them in the interstitial nucleus and in the base of the posterior horn. The cells are triangular and star-shaped. This was found in mammals and birds.

Ramón y Cajal described the basic plan of the posterior commissure as consisting of three bundles: a posterior arcuate, a transverse, and an anterior arcuate. This plan is not so clear in adult mammals, and is poorly developed in man. Kölliker (1891*a*) found no evidence of the posterior arcuate bundle in the lumbar cord of the 4-day-old puppy.

Ramón y Cajal described the posterior arcuate bundle in the chicken embryo, in the rat, dog and "other mammals" as containing the collaterals coming from the fasciculus cuneatus and going on to ramify in the medial part of the opposite posterior horn and the substantia gelatinosa; these fibres lie immediately adjacent to the fasciculus cuneatus, which, in Ramón y Cajal's words, they embrace like a horseshoe. Bechterev (1899) found these fibres most clearly in the lumbar and sacral region. The transverse is the largest of the three bundles, in the mammal. Its fibres run somewhat diagonally. Many of these fibres are the collaterals of fibres of the lateral limiting layer. They traverse the nucleus dorsalis and end in the lateral part of the base of the posterior horn and in the substantia gelatinosa of the opposite side; they give off collaterals. The anterior arcuate fibres run posterior to the central canal and immediately anterior to the nucleus dorsalis. The fibres making up this part of the commissure are both large and fine. These fibres arise in the anterior and the lateral column, and they run to the intermediate nucleus and the substantia intermedia centralis of the opposite side, according to Ramón y Cajal. Bechterev states that they run to the anterior horn.

Ziehen (1899) considered this division of the commissure into three parts to be a schematic exaggeration. He also considered that the transverse bundle does not consist of collaterals of the lateral column fibres but of axons of medial and lateral zonal cells running to the lateral columns.

XUM

Nageotte (1904) described small intrinsic fibres in the median septum. He found them mostly in the sacral region, but also in the cervical region. He thought that they originated in the posterior commissure.

Sosa (1945*a* and *b*) studied in man, other mammals, marsupials, and birds, the small fibres which he called the septal collaterals. These fibres may be the same as the posterior arcuate fibres of Ramón y Cajal; or it may be that both exist. These fibres are mainly non-myelinated collaterals, given off at right angles to the long axis of the fibres of the fasciculus cuneatus; they run within and along the posterior septum; and they terminate within the posterior commissure. Most of them remain ipsilateral, but a few run obliquely through the septum to the other side. Some run to the posterior commissural cells; and some turn laterally at the base of the posterior columns and end around the medial part of the nucleus proprius of the posterior horn, some ipsilaterally, others contralaterally. They are present at all levels of the cord and in the medulla oblongata; they are particularly numerous near the opening out of the fourth ventricle, and in the cervical and lumbar enlargements.

It seems that Ramón y Cajal, Nageotte, and Sosa have probably described the same fibres. Ramon y Cajal thought they were collaterals of the axons of the fasciculus cuneatus going to the contralateral posterior horn, Nageotte thought they were true intrinsic fibres going to commissural cells, and Sosa thought they were collaterals of the fibres of the fasciculus cuneatus going to commissural cells and the posterior horn cells. Ramon y Cajal states that most of the fibres of the posterior commissure are myelineated. Hösel (1900) found that myelination occurs later in the posterior than in the anterior commissure; he found no myelination in the posterior commissure in the sixth fœtal month in man.

The Intrinsic Fibres of the Gray Matter

The shortness of this part of this review is due to the insufficiency of known facts; it is certainly not due to any lack of importance of the subject matter. For it is only recently, and largely due to Laruelle (1937), that a proper concept of the intrinsic fibres of the grey matter has begun to be obtained. It is unfortunate that Laruelle's beautiful photographs of longitudinal sections of the cord taken through different planes have not been published in journals where they would receive the acclaim which they deserve. Laruelle rightly claims that the importance of fibres intrinsic to the grey matter has not been realized. For, as he says, "L'association plurisegmentaire est réalisée, non seulement par les voies cordonales connues, mais par un système de fibres intrinsèques de la substance grise; et les confèrent une fonction conductrice propre à la substance grise de la moelle."

The important subject of collaterals of motor neurones returning into

the grey matter cannot be considered here; for these do not come within our frame of reference, as the parent axons are neither intrinsic to the grey matter nor part of the fasciculi proprii.

The neurones giving rise to fibres of which the entire course remains within the grey matter were first described by Golgi and they are now known usually as Golgi cells Type II; Kölliker called them "Binnenzellen" or "Reflexzellen"; those which cross in the commissure are often called the "commissural cells of Golgi."

Golgi (1880, 1890) described (no species was mentioned) these cells as "ganglion cells, of which the axon breaks up into very thin fibrils, losing its individuality, and in toto going to the formation of the common nerve net." He described them as occurring mostly in the substantia gelatinosa, in the grey matter anterior to the substantia gelatinosa of the posterior horn, some between the anterior and posterior horn, and some in the anterior horn. Kölliker (1891*a*) found them only in the substantia gelatinosa and in the tip of the posterior horn. Bechterev (1899) found them in man in the posterior horn and in the region between the substantia gelatinosa and the nucleus dorsalis; he found only a few in the substantia gelatinosa itself. Ramón y Cajal could find them only in the substantia gelatinosa. No one except Golgi has found them in the anterior horn.

Golgi described some of these cells as sending their processes across the anterior commissure to the grey matter of the opposite side, "contributing to the general nerve net"; he considered that the existence of such cells needed further confirmation. Laura[1] (1881, 1882), who studied the spinal cord of the calf, looked for such neurones, but could not find any.

It is difficult to ascertain from the literature which fibres remain entirely intrinsic to the grey matter, and which fibres arise and terminate in the grey matter, having pursued their course throughout the white matter.

The Posterior Horn

The posterior horn is in the region of the grey matter where the intrinsic fibres of the grey matter are most obvious. Here these fibres are seen to be running in all directions. They are both thick and thin, and most of them are unmyelinated. Most of the fibres are rich in collaterals. An excellent account of the human posterior horn is that of the neurologist who first described it in detail—Lissauer (1886); but although he described the appearance and disposition of the fibres, he did not realize that many of the fibres he was describing are intrinsic. Pearson (1952) investigated the substantia gelatinosa and its relation to the rest of the posterior horn in the baby and the kitten by means of Golgi preparations. He found that the axons of the cells of the substantia gelatinosa "appear to end in

[1]The dates 1881 and 1882 are both given for Laura's work. He published his work in French in 1882, but he had previously presented it in 1881, at an international congress of medicine in London.

XUM

synaptic relation with the pericornual cells and the cells of the nucleus proprius" of the posterior horn.

All workers have observed many cells of Golgi Type II in the posterior horn. The cells of this type send dendrites into the deeper layers of the substantia gelatinosa. Nageotte (1904) concluded from 2 cases with degeneration of the posterior roots that the greater number of the fibres in the stratum spongiosum of the posterior horn are intrinsic.

The Substantia Intermedia Lateralis

Laruelle (1937, 1948) described an intermedio-lateral and an intermedio-medial column. These columns consist of the nuclei with these names and the fibres interlinking the cells of these nuclei in a longitudinal direction. Both columns are present from the eighth cervical to the second lumbar segments, and the intermedio-lateral column is also present in the second, third, fourth and fifth sacral segments; in these segments there are also a few cells similar to those of the intermedio-medial column. Laruelle removed the sympathetic chains bilaterally in a cat, and found that these cells, as well as those of the lateral column, are cells of origin of the sympathetic fibres. In these columns there is no metameric segmentation. There are neurones and fibres connecting the two columns to each other; these are thin and mostly unmyelinated.

Laruelle (1937) described a "véritable noyau commissural postérieur": it is on the same plane in transverse section as the central canal and lateral to the nucleus doralis, and it links the intermedio-lateral columns of the two sides by means of cellulo-fibrillary belts. The cells of this nucleus send out branches cranially, caudally, and across the commissure to the other side.

Fine fibres "passing between the postero-lateral region of the grey matter and the anterior horn cells" were found by Keene and Hewer (1931) to myelinate between the 16th and the 22nd weeks.

The Grey Commissure

The grey commissure (commissura intragrisea or intracentralis) is most developed in the cervical and lumbar enlargements and the sacral cord; it is poorly developed in the thoracic cord; according to Müller, it does not exist in the conus. It is described by Barbé (1938) as consisting of two parts, the two being separated by the central canal.

The grey commissure is composed of the collaterals of posterior root fibres, of collaterals, axons, and dendrites of the neurones of the substantia intermedia centralis, of fibres of the cornu-commissural tract, of a few dendrites of neurones of the posterior horns, and possibly collaterals of axons of the posterior parts of the lateral columns and of some axons of the anterior horns.

Laruelle (1937) described unmyelinated fibres crossing in this com-

TABLE III. FASCICULI PROPRII OF THE SPINAL CORD IN MAN

	Anterior ground bundle	*Lateral ground bundle*	*Posterior ground bundle*	*Lissauer's tract*	*Cornu-commissural tract*	*Comma tract* *	*Septo-marginal tract*	*Anterior commissure*	*Posterior commissure*	*Intrinsic fibres of grey matter*
Cells of Origin . .	±	+	±	±	±	+	±	+	+	±
Course	±	+	±	+	+	+	+	+	+	±
Direction of conduction . .	±	±	±	+	+	+	+	+	+	±
Termination . .	±	±	±	+	−	±	±	±	±	±
Size of fibres . .	±	+	+	+	±	−	−	+	+	±
Myelination . .	+	+	+	+	±	−	±	±	±	−

*Although this tract probably consists entirely of extrinsic fibres, it is included in this table, as up to now it has always been grouped with the intrinsic fibres of the cord.

missure immediately posterior to the central canal. These fine fibres arise in his "noyau commissural postérieur" and link together the two intermedio-lateral columns. He described the cells of the intermedio-lateral columns as themselves sending unmyelinated fibres across the grey commissure, immediately posterior to the central canal.

The fibres in this commissure are fine. Many of them are unmyelinated and many measure 2 to 3 μ. According to Ziehen (1899) some of them measure 7 μ.

We would like to emphasize, as we did in our review of what is known about the long descending tracts in man, that material which can be used to fill the gaps in our knowledge of the anatomy of the intrinsic fibres of the cord must come into the hands of neurologists and pathologists every day; at present this material is usually wasted.

How much remains to be found out can quickly be seen by looking at Table III. The + indicates that the point tabulated is known, the − indicates that it is unknown, and the ± indicates that it is unverified.

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XUM

OCULOMOTOR RESPONSES ON VESTIBULAR STIMULATION OF MONKEYS WITH LESIONS OF THE BRAIN-STEM[1]

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ALTERATIONS in the response to vestibular stimulation are often difficult to interpret in terms of localization of lesion. The defects may be in the oculomotor, postural, or autonomic component of the response. Theoretically, a lesion anywhere along the afferent pathway extending from the semicircular canals through the eighth cranial nerve into the vestibular nuclei may produce a defect in reaction in any one or all three components mentioned. Moreover, a lesion situated beyond the vestibular nuclei, in the fibre pathways and internuncial neurons of the brain-stem which participate in the eye, head, neck, body and autonomic mechanisms may also produce a partial defect in response. Experimentally there have been sporadic investigations on the effect of lesion on the vestibular response but there has been no systematic study of the whole brain-stem. The historical information on this subject might be obtained by consulting the comprehensive book written by Spiegel and Sommer, 1944. Following this compilation there has been little in the literature which would appear to be significant.

The purpose of this communication is to present data obtained on vestibular stimulations in monkeys who had discrete electrolytic lesions in the brain-stem. In particular we concentrated on the deficits which occurred in the horizontal component of the oculomotor response, although defects in the vertical component were observed with special methods of testing. We will not attempt to evaluate alterations in posture, locomotion, autonomic function or in vision which often occur as a result of these stimulations.

METHODS AND MATERIALS

70 monkeys (*Macaca mulatta*) were studied before and after small circumscribed lesions were made at specified points in the brain-stem. By making one single lesion at different points in each of the monkeys it was thus possible to explore the entire brain-stem. In addition to these 70 monkeys, we analysed the data of experiments performed in other macaques with lesions in the median longitudinal fasciculus,

[1]This investigation was supported (in part) by a research grant No. B–294 from the National Institute of Neurological Diseases and Blindness, Public Health Service.

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XUM

central tegmental fasciculus and other structures. These experiments were reported in part in other communications. Stereotaxic instrument was used to direct the electrodes and electrolytic lesions were made. The technique was described in detail in previous reports. Vestibular functions were tested usually by cold caloric water irrigations of the ear canals. In most instances 20 c.c. of water were injected for a period of 10 seconds. In several monkeys warm water was also used for irrigations by the same method. Nystagmus was recorded electro-oculographically by methods previously described. The caloric examinations were executed in an illuminated environment and in total darkness. All the monkeys had vestibular turning tests. These were performed in an illuminated environment. Ten turns were made in 10 seconds. Every monkey was thus tested while in the erect position. Some were also tested while they were in the supine, prone or lateral positions.

In some monkeys the vestibular function, caloric and turning tests were also carried out under long and short periods of barbiturate narcosis. After an adequate interval of observation, when the neurologic status remained constant for several weeks, the monkey was sacrificed. The anatomy of the brain-stem was studied with myelin sheath stains and the site of the lesion identified in serial sections.

The results obtained using cold or warm water irrigations in the normal monkey are described in Table IA. Oculomotor (tonic deviation and nystagmus) and other behavioural changes were noted but only the former will be reported here. Several monkeys had bilateral cold as well as warm caloric stimulations. The ocular responses are recorded in Table IB. The results of the oculomotor responses obtained on rotational tests in various positions of the normal monkey are recorded in Table II. The head, chin and eye postures were noted during and after the turning tests were made.

TABLE I.—OCULOMOTOR RESPONSES ON CALORIC (COLD OR WARM) STIMULATION IN THE NORMAL MONKEY

The eye movements consisted of two vectors, a tonic deviation in one direction and a nystagmus in the opposite direction. The nystagmus in turn was manifested by a slow component in the direction of tonic deviation and a fast component in the opposite direction. All oculomotor responses were analysed in terms of the direction of a particular vector in the horizontal or vertical plane.

Caloric stimulus	*Ear stimulated*	*Oculomotor response*	
		Right vector	*Left vector*
A.—STIMULATION OF ONE EAR AT A TIME WITH BODY AND HEAD ERECT			
Cold	Right	Tonic deviation to right	Nystagmus, fast component to left
Warm	Right	Nystagmus, fast component to right	Tonic deviation to left
Cold	Left	Nystagmus, fast component to right	Tonic deviation to left
Warm	Left	Tonic deviation to right	Nystagmus, fast component to left
B.—SIMULTANEOUS STIMULATION OF BOTH EARS			
		Upward vector	*Downward vector*
Cold	Bilateral	Nystagmus, fast component upward	Tonic deviation downward
Warm	Bilateral	Tonic deviation upward	Nystagmus, fast component downward

XUM

TABLE II.—OCULOMOTOR RESPONSES AFTER ROTATIONAL STIMULATIONS IN NORMAL MONKEY

Direction of rotation	*Post rotational oculomotor responses*	
	Right vector	*Left vector*
	A.—BODY AND HEAD ERECT	
Clockwise	Tonic deviation to right	Nystagmus, fast component to left
Counterclockwise	Nystagmus, fast component to right	Tonic deviation to left
	B.—BODY AND HEAD SUPINE	
Clockwise	Rotary nystagmus with fast component to right and counterclockwise	Tonic deviation to left
Counterclockwise	Tonic deviation to right	Rotary nystagmus with fast component to left and clockwise
	C.—BODY AND HEAD IN RIGHT LATERAL POSITION	
	Upward vector	*Downward vector*
Clockwise	Tonic deviation upward	Nystagmus, fast component downward
Counterclockwise	Nystagmus, fast component upward	Tonic deviation downward
	D.—BODY AND HEAD IN LEFT LATERAL POSITION	
Clockwise	Nystagmus, fast component upward	Tonic deviation downward
Counterclockwise	Tonic deviation upward	Nystagmus, fast component downward

RESULTS

In evaluating our results we took into consideration the alertness of the animal and the possibility that the ear drums might have been punctured on either caloric douching or by the insertion of ear plugs when the stereotaxic instrument was applied. In controlled studies where no lesions of the brain-stem were made we did not find that a punctured ear drum *per se* caused a decrease or absence of oculomotor response to caloric stimulation. In fact, there was usually a quicker appearance and more prolonged nystagmus response.

We also considered the effect of visual stimuli on the oculomotor response in our experiments. It is well known that the nystagmus induced by vestibular stimulation in an illuminated environment is not as enduring as when the animal is tested in total darkness. Moreover the optokinetic effect induced by the movement of the body and eyes is found to influence the vestibular nystagmus. With the method of electric recording of eye movements we were able to compare the effects of caloric stimulation in dark and illuminated environment. The nystagmus induced in darkness

XUM

was much more prolonged and conspicuous than the reaction obtained in an illuminated surrounding. This difference was true for the normal as well as for the experimental animal. However, it is significant that the pattern of the abnormal oculomotor responses in monkeys with lesions in the brain-stem remained the same in all degrees of illumination. Whereas caloric stimulations were performed in a light and dark room, we did the rotational tests only in an illuminated environment. Rotational tests were not made in darkness because the turning apparatus was not as yet adapted for electrooculography, which records eye movements continuously. The advantage of the caloric over the turning tests is that the thermal stimulations could be performed in darkness, the eye movements being recorded electrographically. The pattern of the abnormal oculomotor response depended on the location and size of the lesion and the time of the examination. The patterns obtained on thermal and rotational stimulations are described according to location of lesion. These lesions may be divided into groups rostral and caudal to the level of the oculomotor-trochlear nuclei.

(A) *Rostral Lesions*

In 9 monkeys, lesions, 2–4 mm. in diameter, situated in the median and paramedian portions of the superior mid-brain, such as in the region of the red nucleus (fig. 1, Plate LV) or more rostrally in the fields of Forel or even in the ventral thalamic area (fig. 2) resulted in slight and not very enduring defects in the oculomotor response on vestibular stimulation. The duration of the contralateral ocular defects was only a matter of one to five days. After this period the monkey seemed normal. The larger the lesion the more enduring was the defect. Of significance in this group is that all the defects in the nystagmus or tonic deviation occurred in a direction opposite to the side of the lesion. Thus, in a monkey with a lesion in the left mid-brain at the level of the red nucleus (fig. 1), cold caloric stimulation of the left ear or turning tests resulted either in a defect of the quick component or an irregularity with decreased amplitude of the nystagmus to the right. Occasionally there was a shimmering nystagmus. The results obtained on caloric tests are summarized in Table III, and on the rotational tests in Table IV.

In these monkeys there was some evidence of defect in tonic deviation but not in the slow component of the nystagmus. These animals showed a gaze preference toward the side of the lesion. In 3 monkeys 2·0 mm. lesions involving principally the left fields of Forel and some of the adjacent structures caused a defect in the vestibular response, manifested by decreased, unsustained and irregular nystagmus to the right. Of interest is that disturbances in vertical plane could also be elicited. Thus monkeys in this group when tested in the erect position during the post-

PLATE LV

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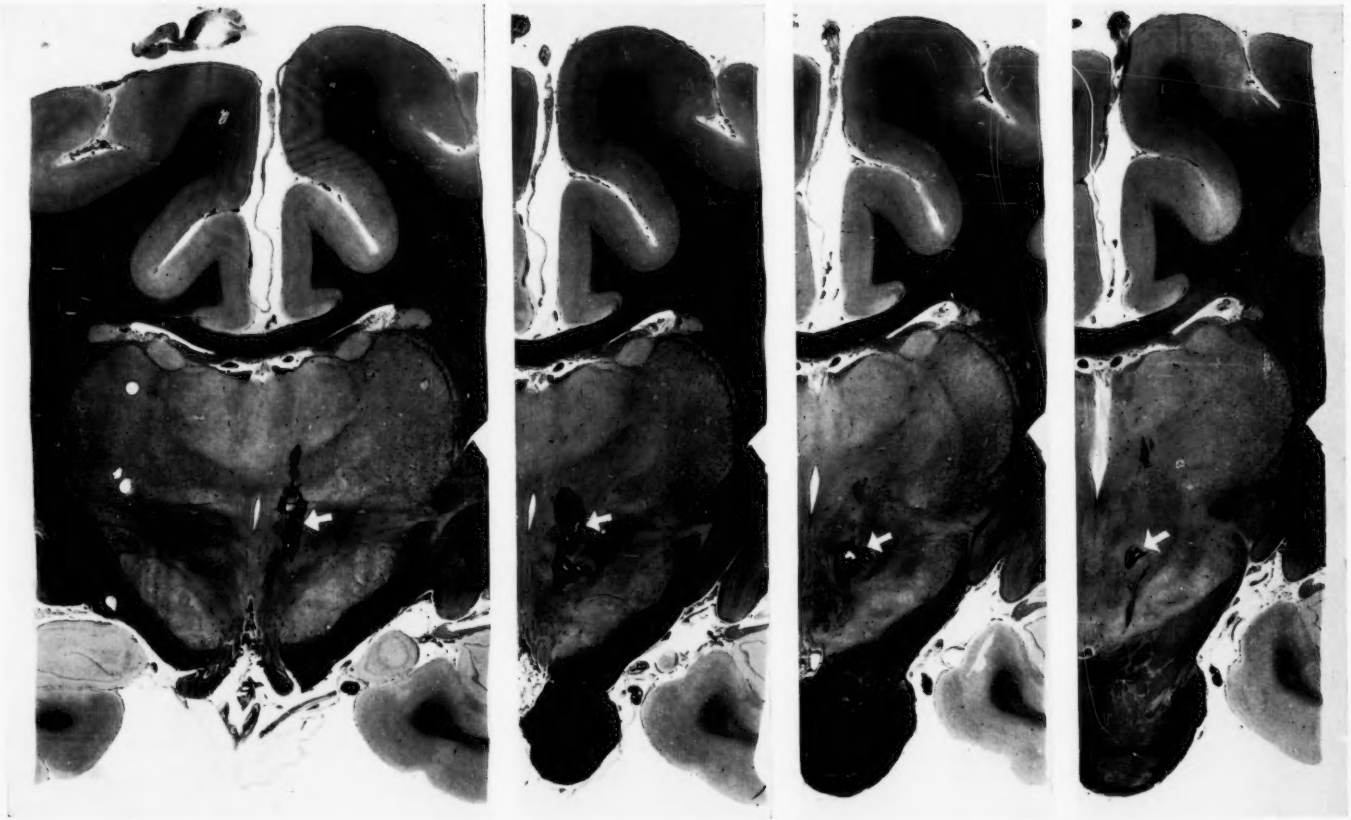

FIG. 1.—Monkey No. 119. Serial section showing lesion (arrows) implicating red nucleus, fields of Forel, zona incerta and a small region of ventral thalamus.

To illustrate article by Stefan Shanzer and Morris B. Bender.

PLATE LVI

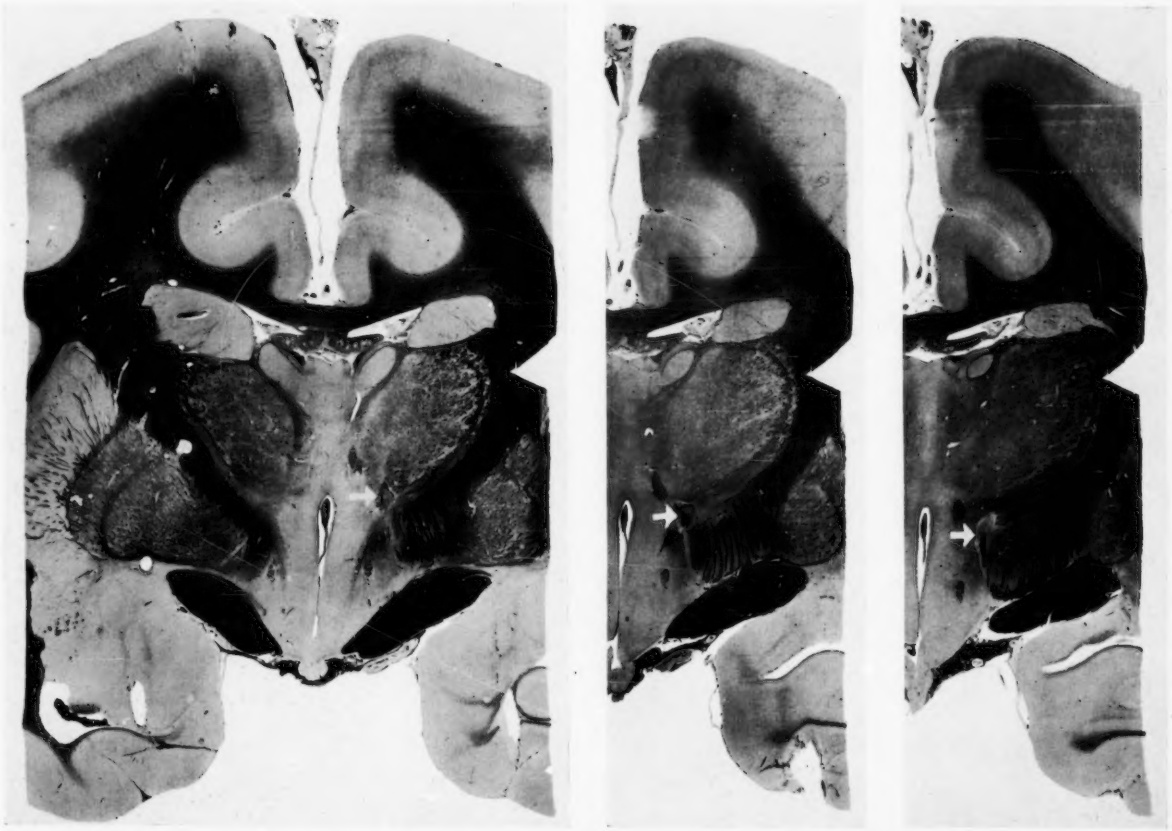

FIG. 2.—Monkey No. 113. Serial sections (arrows) showing lesion implicating part of the fields of Forel and zona incerta.

To illustrate article by Stefan Shanzer and Morris B. Bender.

PLATE LVII

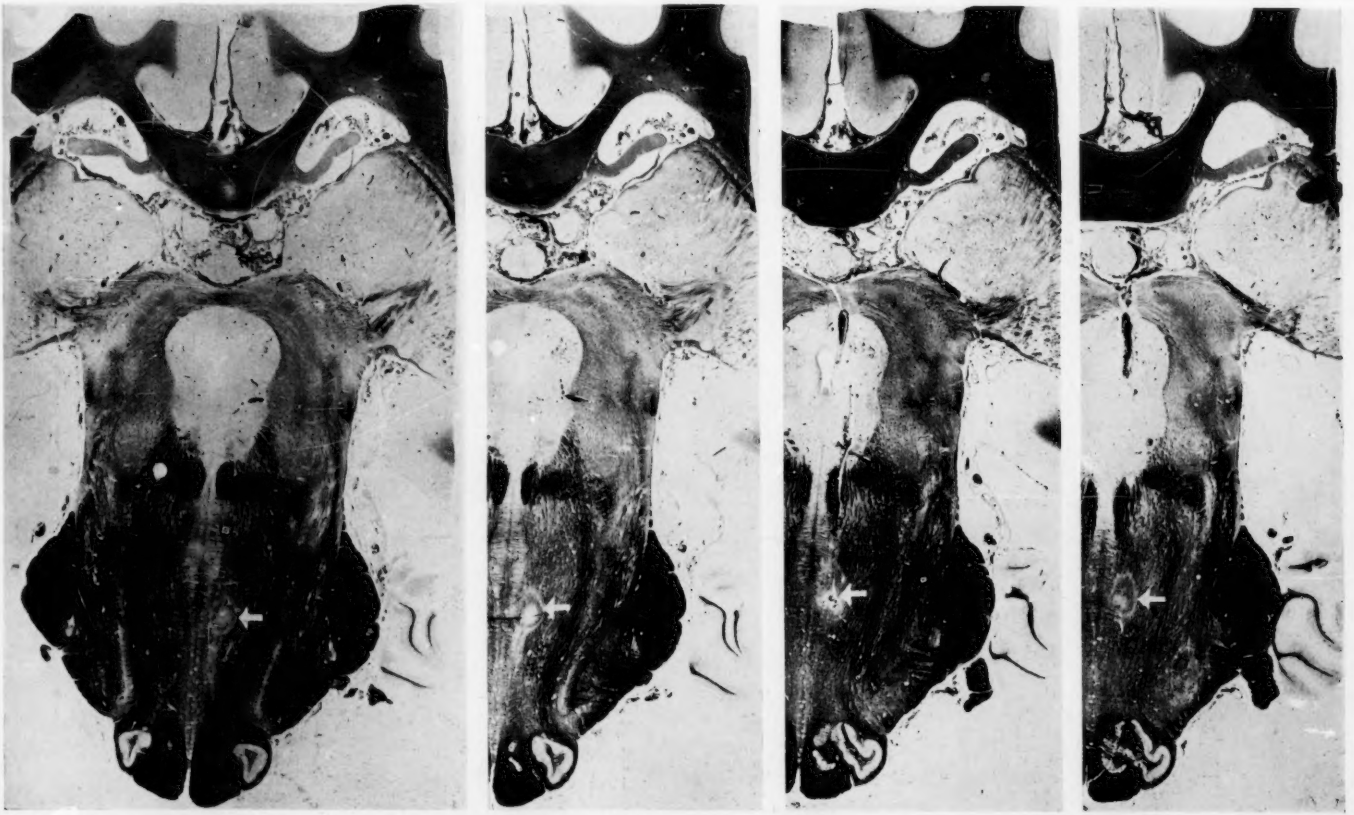

FIG. 3.—Monkey No. 72. Serial sections showing spherical lesion (arrows) implicating parts of the paramedian pontine reticular formation.

To illustrate article by Stefan Shanzer and Morris B. Bender.

FIG. 4.—Monkey No. 104. Serial section showing lesion (arrows) implicating part of the vestibular complex.

To illustrate article by Stefan Shanzer and Morris B. Bender.

PLATE LIX

FIG. 5.—Monkey No. 102. Serial sections of lesion (arrows) implicating part of the vestibular complex.

To illustrate article by Stefan Shanzer and Morris B. Bender.

FIG. 6.—Monkey No. BS 23. Lesion (arrows) implicating both medial longitudinal fasciculi.

To illustrate article by Stefan Shanzer and Morris B. Bender.

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PLATE LXI

FIG. 7.—Monkey No. 97. Lesions (arrows) involving both superior colliculi.

To illustrate article by Stefan Shanzer and Morris B. Bender.

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rotational state showed defects in contralateral horizontal movements as described in Table IVA and B. When tested with the head and body in a lateral position, the post-rotational status showed a significant absence of

TABLE III.—OCULOMOTOR RESPONSES ON CALORIC STIMULATION IN MONKEYS WITH A DISCRETE 2–4 MM. LESION IN THE SUPERIOR BRAIN-STEM LEFT SIDE. ALL TESTS WERE PERFORMED WITH BODY AND HEAD ERECT

Caloric stimulus	*Ear stimulated*	*Oculomotor response*	
		Right vector	*Left vector*
	A.—UNILATERAL STIMULATION OF EITHER EAR		
Cold	Right	No tonic deviation to right	Nystagmus, fast component to left
Cold	Left	Defective nystagmus, fast component to right	Tonic deviation to left
Warm	Right	Defective nystagmus, jerk to right	Tonic deviation to left
Warm	Left	No tonic deviation to right	Nystagmus, fast component to left
	B.—BILATERAL SIMULTANEOUS STIMULATION OF THE EARS		
		Upward vector	*Downward vector*
Cold	Bilateral	Nystagmus, fast component upward	Poor tonic deviation downward
Warm	Bilateral	Tonic deviation upward	Defective nystagmus downward

TABLE IV.—ROTATIONAL TESTS IN MONKEYS WITH LESIONS INVOLVING LEFT FIELDS OF FOREL OR RED NUCLEUS. OBSERVATIONS WERE MADE ON POST ROTATIONAL OCULOMOTOR RESPONSES

Direction of Rotation	*Post rotational oculomotor response*	
	Right vector	*Left vector*
	A.—MONKEY SITTING WITH BODY AND HEAD ERECT	
Clockwise	Defective tonic deviation to right	Nystagmus, fast component to left
Counterclockwise	Defective nystagmus to right (shimmering)	Tonic deviation to left
	B.—MONKEY LYING IN RIGHT LATERAL POSITION	
	Upward vector	*Downward vector*
Clockwise	Tonic deviation upward	Defective nystagmus downward (shimmering)
Counterclockwise	Normal nystagmus, fast component upward	Defective tonic deviation downward
	C.—MONKEY LYING IN LEFT LATERAL POSITION	
	Upward vector	*Downward vector*
Clockwise	Nystagmus, fast component upward	Defective tonic deviation downward
Counterclockwise	Tonic deviation upward	Defective nystagmus downward (shimmering)

XUM

tonic deviation or of the nystagmus in a downward direction (Table IVB and C). There were no abnormalities in the upward direction. Similarly, simultaneous stimulation of both ears with cold water resulted in poor tonic deviation in a downward direction. Simultaneous irrigation with warm water gave only poor or shimmering nystagmus on downward gaze (Table IIIB). These findings are a clear example of a defect in oculomotor response in the vertical plane.

(B) *Caudal Lesions*

In 26 monkeys, 1–2 mm. lesions were made in the paramedian zone of the tegmentum of the brain-stem below the levels of the trochlear nuclei. A typical lesion is illustrated in fig. 3. Defects in the oculomotor response on vestibular stimulations were noted in all animals with lesions situated in the paramedian zone of the tegmentum, at levels between the trochlear and vestibular nuclei. In these monkeys caloric or rotational stimulations elicited defects in tonic deviation and in the quick component of induced nystagmus when the direction of movement was to be to the side of the lesion. Hence, when an electrolytic lesion was made 1 mm. to the left of the mid-line, there was an alteration of the vestibulo-ocular response to the left. The defect in the nystagmus, beating toward the side of the lesion, varied in degree of amplitude, regularity and duration of the nystagmus. The larger the lesion the more severe and enduring was the alteration in the oculomotor response. The defect in tonic deviation of the eyes was most apparent on the first day after the lesion was made.

TABLE V.—VESTIBULO-OCULOMOTOR RESPONSES ON CALORIC STIMULATION IN MONKEYS, WITH 1–2 MM. LESIONS IN THE LEFT PARAMEDIAN ZONE CAUDAL TO THE TROCHLEAR NUCLEUS. ALL TESTS WERE PERFORMED WITH BODY AND HEAD ERECT.

Caloric stimulus	*Ear stimulated*	*Oculomotor response*	
		Right vector	*Left vector*
	A.—UNILATERAL STIMULATION OF EITHER EAR		
Cold	Right	Marked tonic deviation to the right	No nystagmus to the left
Warm	Right	Good nystagmus to the right	Poor or no tonic deviation to the left
Cold	Left	Good nystagmus to the right	Defective tonic deviation to the left
Warm	Left	Marked tonic deviation to the right	No nystagmus to the left
	B.—BILATERAL SIMULTANEOUS STIMULATION OF THE EARS		
		Upward vector	*Downward vector*
Cold	Bilateral	Defective nystagmus, fast component upward	Tonic deviation downward
Warm	Bilateral	Poor tonic deviation upward	Nystagmus, fast component downward

It became less pronounced during the ensuing days of recovery. In some monkeys complete recovery did not occur even after one year. The types of oculomotor deficits induced by cold or warm caloric stimulations in the right or left ear in a monkey with a lesion in the left paramedian zone are summarized in Table V. The rotational tests, with the head erect in this group of monkeys, elicited defects of the ocular responses in the horizontal plane as recorded in Table VIA. Defects in the vertical plane were elicited

TABLE VI.—POST ROTATIONAL OCULOMOTOR EFFECTS IN MONKEYS WITH 1–2 MM. LESIONS IN THE LEFT PARAMEDIAN ZONE OF TEGMENTUM OF PONS

Direction of Rotation	*Post rotational oculomotor response*	
	Right vector	*Left vector*
A.—MONKEY SITTING WITH BODY AND HEAD ERECT		
Clockwise	Tonic deviation to right	No nystagmus to left
Counterclockwise	Good nystagmus to right	No tonic deviation to left
B.—MONKEY LYING IN RIGHT LATERAL POSITION		
	Upward vector	*Downward vector*
Clockwise	? defective tonic deviation upward	Nystagmus, fast component downward
Counterclockwise	Defective nystagmus upward	Tonic deviation downward
C.—MONKEY LYING IN LEFT LATERAL POSITION		
	Upward vector	*Downward vector*
Clockwise	Defective nystagmus upward	Tonic deviation downward
Counterclockwise	? defective tonic deviation upward	Nystagmus, fast component downward

by placing the monkey on one of its sides or by double simultaneous caloric stimulations. There was impairment of upward component of the responses. Nystagmus and at time the tonic upward deviation were defective. The results are recorded in Table VB and Table VIB and C.

Under barbiturate narcosis (sodium amytal 0·1 gramme injected intravenously) all spontaneous or induced nystagmus is abolished in the normal monkey. In monkeys with a lesion in the paramedian zone below the oculomotor nucleus, amytal narcosis reveals a defect in tonic deviation as described above. In addition it was noted that while asleep they manifest a forced deviation of the eyes to the side opposite to the lesion. In some monkeys the decrease in tonic deviation under barbiturates was particularly evident in the turning tests. There was no induction of tonic deviation to the side of the lesion. There was good deviation to the normal side. In others the reverse occurred—the defect in tonic deviation lessened or disappeared under light anæsthesia. Thus, tonic deviation occurred on vestibular stimulation in the narcotized but not in the alert preparation. Deep barbiturate narcosis abolished the nystagmus as well as tonic

XUM

deviation, no matter which ear was stimulated in the experimental or normal monkey.

(C) *Vestibular Lesions*

Lesions in the vestibular nuclei were made in 5 monkeys. From the available anatomic specimens we found that no one lesion was large enough to destroy all of the superior, triangular and lateral components of the nucleus. The location and configuration of these nuclear masses are so complex that it would be impossible to destroy the whole vestibular nucleus without damaging adjacent structures. Nevertheless, when part of the nucleus was damaged, as illustrated in figs. 4 and 5, there resulted head inclination usually to the side of the lesion, and spontaneous nystagmus to the other side. There were also variable defects in optokinetic nystagmus and optokinetic after-nystagmus. Thus, in a monkey with a lesion involving part of the left vestibular nucleus, the head inclined to the left, there was spontaneous nystagmus to the right and the optokinetic nystagmus and optokinetic after-nystagmus were defective from left to right. Caloric stimulation in the left ear produced no ocular response; the nystagmus to the right produced by the lesion was unchanged and there was no induction of tonic deviation to the left. Warm caloric stimulation of the left ear produced weak nystagmus to the left. Cold or warm caloric stimulation of the right ear resulted in prompt oculomotor and postural response. Turning tests with monkey erect showed defects in tonic deviation as well as in the quick component of nystagmus to the left. The oculomotor data we obtained with small lesions were not consistent. We intend to compare these findings with those produced by much larger lesions in the vestibular nuclei. These observations will be published in a separate communication.

(D) *Lesions in the rest of the Brain-stem*

In 30 monkeys 2–4 mm. lesions were made in areas of the brain-stem outside of the vestibular nuclei and paramedian zone of the tegmentum. In these animals there were no demonstrable alterations in the nystagmus (quick component) or tonic deviation (slow component) in response to vestibular stimulation by caloric or turning methods. Electrolytic defects in such structures as the reticular formation situated at 2·5 mm. or more lateral to the mid-line, the central grey matter, central tegmental fasciculus, the corticospinal system of fibres or the superior olives produced no abnormalities in response to vestibular stimulation. (The locations of the lesions are illustrated in the drawn serial diagrams of the brain-stem fig. 8). Since the size of the defect was rarely greater than 3·0 mm. we are unable to say whether larger zones or multiple small areas of destruction outside of the paramedian zone would not produce vestibulo-oculomotor deficits. Also we have but little information on the effects of bilateral lesions. Such investigations are beyond the scope of this series of experiments.

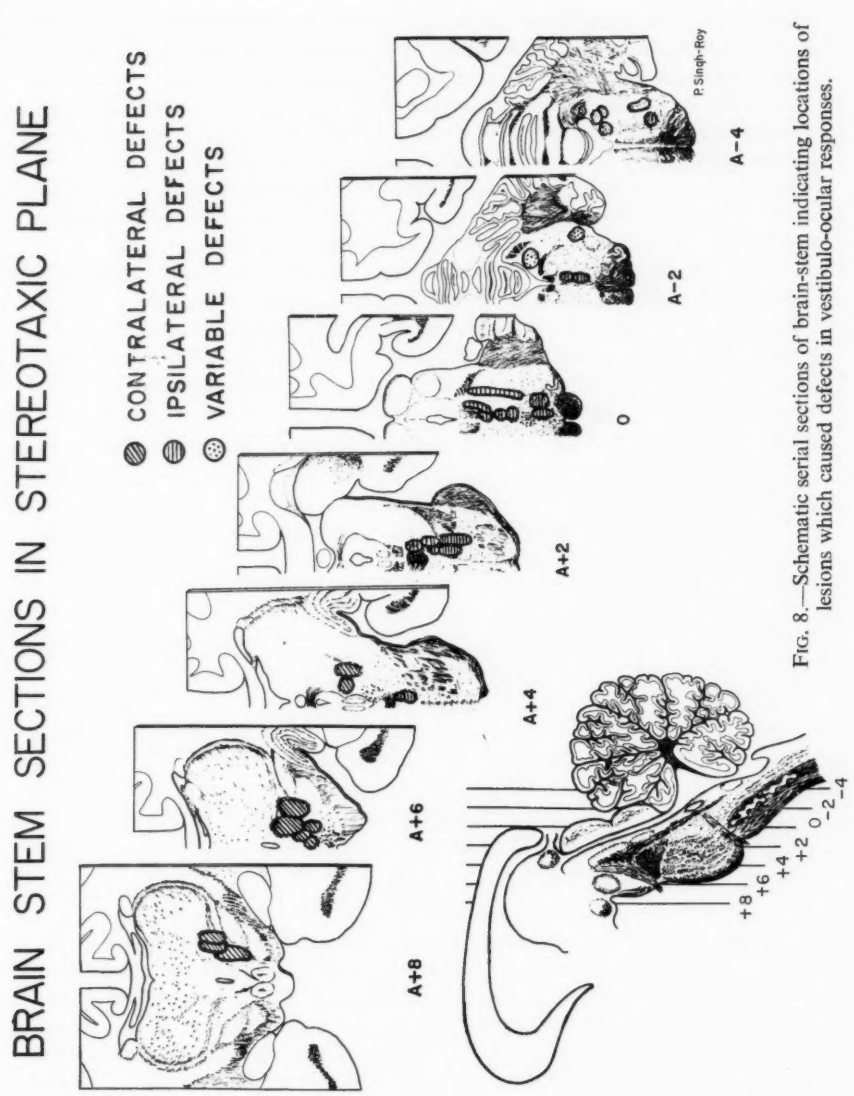

FIG. 8.—Schematic serial sections of brain-stem indicating locations of lesions which caused defects in vestibulo-ocular responses.

Lesions in the median longitudinal fasciculus, as illustrated in fig. 6, produced the syndrome usually observed after such lesions, namely dissociated eye movements and monocular nystagmus in the horizontal plane (Bender and Weinstein, 1944). On lateral gaze there was defective

movement with minimal or no nystagmus in the adducting eye and good outward deviation with nystagmus in the abducting eye. Convergence was preserved and there was slight nystagmus on upward gaze. On vestibular stimulation with cold water and head erect in these monkeys, there occurred a nystagmus with the quick component being most manifest in the abducting eye. Tonic deviation was not altered except in the adducting eye. Barany turning tests with head erect produced the expected responses. The paralysis of adduction and monocular (greater) nystagmus in the abducted eye became accentuated by the caloric or turning tests. It should be noted that a lesion 1·0 mm. in diameter extending across the entire width of the median longitudinal fasciculus at any level along its course between the third and sixth nerve nuclei did not cause paralysis of conjugate ocular gaze. In these monkeys there was no loss of optokinetic nystagmus, afternystagmus or impairment of the aforementioned types of vestibulo-oculomotor responses.

Lesions of one or even larger than 2 mm. in diameter within the brachium conjunctivum situated in the brain-stem produced no changes in the oculomotor response on vestibular stimulation. Cold caloric or turning stimulation tests produced no apparent abnormalities in the tonic deviation or nystagmus response. The rest of the cerebellar peduncles, vestibulo-cerebellar pathways as well as the cerebellum itself were not adequately investigated in this study to warrant a report.

In experiments with lesions of the superior colliculi (fig. 7) we found no interference with the vestibular oculomotor response (Bender, Pasik, T., and Pasik, P., 1957). Caloric or turning stimulation tests produced normal nystagmus even when the greater portion of the superior colliculi were destroyed. For that matter lesions in the inferior colliculi also failed to show a defect in ocular response to vestibular stimulation. The observations on oculomotor functions in monkeys with lesions of the superior colliculi will be reported in a separate communication.

Discussion

Preliminary studies have shown that small lesions (1 to 2 mm. in diameter) in the paramedian zone of the tegmentum of the brain-stem caudally to the level of the trochlear nucleus resulted either in paralysis or paresis of ipsilateral horizontal ocular deviation (Teng, Shanzer and Bender, 1956), defects in optokinetic response (Teng, Shanzer and Bender, 1958) and optokinetic afternystagmus (Shanzer, Teng, Krieger and Bender, 1958). This ipsilateral ocular gaze palsy varied in duration. Lesions rostral to the level of the oculomotor trochlear nucleus complex resulted in defects in contralateral ocular deviations and in optokinetic response. These contralateral defects were more transient and less intense than the ipsilateral defect produced by lesions caudal to the trochlear

nucleus. Lesions in the region of the vestibular nuclei caused variable and transient defects. The sites of lesions in the brain-stem causing impairment in conjugate eye movements are illustrated in the diagram of fig. 8. There were no defects in oculomotor functions with lesions in other areas of the brain-stem except in regions of the oculomotor and abducens nucleus, their rootlets (Bender and Weinstein, 1943), in the median longitudinal fasciculus (Bender and Weinstein, 1944) as previously described.

In comparing the present results obtained in experiments on vestibular stimulation tests with those of previous investigations on oculomotor functions using optokinetic stimulation tests, it is apparent that the defects in the ocular response to vestibular stimulation happen to be caused by the same lesion which results in defects in optokinetic nystagmus and optokinetic afternystagmus. From this, one would conclude that the defects in the particular ocular response, observed in each of the experimental test situations, are due to lesions in the oculomotor efferent pathways rather than in the afferent vestibular or visual system. This does not mean that lesions in the oculomotor pathways abolish vestibular response. They only interfere with the motor component of the vestibulo-ocular effect.

Of interest is that lesions in the paramedian zone seem to alter ocular movements in the horizontal plane. This becomes evident because the methods we employ in conventional caloric stimulation induce horizontal eye movements. However, if we change the method and employ a technique which induces ocular movements in the vertical plane, defects in the vertical plane become apparent. With the monkey lying on one of its sides, rotation will elicit defects in a downward direction if the lesion is above the level of the oculomotor nucleus and in an upward direction if the lesion is at or below the level of the trochlear nucleus. Defects in the vertical plane may also be elicited if bilateral stimultaneous caloric stimulations of the ears were done routinely. Thus, if bilateral cold caloric stimulation fails to induce nystagmus in an upward direction, one should suspect a disturbance of upward eye movement. Conversely, if bilateral warm caloric stimulation of the ears fails to induce downward nystagmus, then one must consider a defect in a downward eye movement. From the foregoing it is obvious that the pattern of the defect in oculomotor function induced by vestibular stimulation depends not only on the location, size and duration of the lesion but also on the method of examination. For that matter the pattern may depend on other variables such as state of alertness, age of the animal, the type and intensity of afferent stimuli (visual or cochlear) which are present while vestibular stimulation is performed (Spiegel and Scala, 1947). These are but a few variables which one must consider in interpreting results.

Some questions which arise from all of these studies are (*a*) where in

XUM

the nervous system do the vestibular nuclei fire or stimulate the oculomotor mechanism ? (*b*) Is this accomplished in the brain-stem at the level of the vestibular nuclei or cells in the reticular formation ? (*c*) Is there a diffuse afferent pathway from the vestibular nuclei through the brain-stem which projects directly or indirectly upward to the basal ganglia and cerebum, ultimately connecting with the oculomotor system ? Then there is the question as to the direction of flow of impulses along the oculomotor pathways in the brain-stem. What is the locus of the pathway which conducts vestibulo-oculomotor impulses in an ascending direction ? Are there fibres which mediate vestibulo-oculomotor impulses from the basal ganglia level or the fields of Forel in a caudal direction ? Where does integration of these systems occur ? These are old questions which have been raised by various investigators over a period of years. Our present experiments do not answer these. For that matter neither do the older methods of anatomic degeneration experiments nor the tracing of fibres in the brain-stem from the vestibular nuclei contribute greatly to the questions. Spiegel, 1944, who has done extensive investigation on the vestibulo-oculomotor systems discusses the anatomy and physiology of the central pathway of these systems in great detail. However, it is doubtful whether all the factual data and theories presented can answer the questions raised.

Many of the theoretical explanations offered by various investigators are old, fixed and unchallenged. Thus, the median longitudinal fasciculus and superior colliculus are structures often referred to as being "crucial" in vestibulo-oculomotor integration. Yet, from our researches, it is clear that discrete lesions in either of these structures do not interfere with the oculomotor response to vestibular stimulation. Moreover, electric stimulation of the median longitudinal fasciculus never causes conjugate ocular deviation or nystagmus. Similarly, electric stimulation of the colliculi in the anæsthetized animal caused no horizontal or vertical eye movements, although in the alert preparation there were some ocular deviations on occasions. As for determination of the central pathways of the vestibular and visual oculomotor impulses, the "multiple methods" study might be more revealing than the conventional single approach.

Our present data derived from observations of patterns of ocular behaviour caused by defect in structure and modified by a variety of methods of testing during a period of recovery do not offer immediate solution to problems in neurophysiology. However, these data and tests may have some clinical value. If we may generalize from monkeys to man, and we have done so in other studies of lesions of the brain-stem with some degree of accuracy, one might assume that a defect in oculomotor response to vestibular stimulation implies a lesion within the oculomotor system. We have found that in man a lesion in the paramedian zone of the tegmentum of the pons causes among various

dysfunctions, defects in the oculomotor response to vestibular stimulation. The disorder is almost identical as in the experimental monkey. In some patients there may be in addition to the oculomotor deficit variable decrease in autonomic and postural response on vestibular stimulation. However, lesions in the brain-stem of man are rarely well localized or sufficiently restricted to the areas we have been investigating. Therefore, it is not easy to compare the vestibulo-ocular symptomatology of small focal electrolytic lesion in the monkey with the irregular and larger lesions caused by disease in man. Despite this difference in size of defect in structure, it is possible to approximate and predict the site of the disease in a patient who manifests the types of oculomotor dysfunction we have observed in a monkey with known location of the electrolytic lesion.

Summary

(1) The oculomotor responses to vestibular stimulation were studied in 70 monkeys with lesions in the brain-stem. A variety of methods of vestibular testing were employed. Caloric (cold or hot) as well as rotational (body erect or laterally placed) stimulations were carried out before and serially after lesions were made.

(2) Electrolytic lesions (2–4 mm.) above the level of the oculomotor nerve nucleus caused defects in vestibulo-ocular response in a horizontal direction which was contralateral to the side of the lesion. With the monkey in the lateral position, rotational tests also demonstrated defects in the vertical plane; there was decreased to absent downward nystagmus.

(3) Small (1–2 mm.) lesions below the level of the trochlear nucleus produced defects in the vestibulo-ocular response in a horizontal direction which was ipsilateral to the side of the lesion. With the monkey in the lateral position rotation tests also demonstrated defects in the vertical plane; there was decreased or absent upward nystagmus.

(4) The defects in ipsilateral eye movements were most conspicuous and found only in lesions of the paramedian zone of the tegmentum of the brain-stem, situated between the levels of the trochlear and vestibular nuclei.

(5) Lesions which involved only part of the vestibular nuclei produced a loss of responses when the ear on the side of the lesion was calorically stimulated. Rotational tests showed defects in tonic deviation as well as in the quick component of nystagmus in the direction of the vestibular nucleus lesion.

(6) Comparable sized (1–4 mm.) lesions in other areas of the brain-stem produced no manifest defects in the oculomotor response on vestibular stimulations.

XUM

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NOTICES OF RECENT PUBLICATIONS

SPEECH AND ITS DISTURBANCES

Speech and Brain-Mechanisms. By WILDER PENFIELD and LAMAR ROBERTS. 1959. Pp. 286. Princeton University Press, Princeton, New Jersey, and Oxford University Press, London. Price 35s.

Handbook of Speech Pathology. Edited by LEE EDWARD TRAVIS, Professor of Psychology and Speech, and Director of the Speech and Hearing Clinic, University of Southern California. 1959. Pp. 1088. Peter Owen, Ltd. Price 84s.

Penfield and Robert's book is "a discussion of the cerebral mechanisms of speech, the learning of language and the teaching of language," based upon a ten years' study of patients passing through the Montreal Neurological Institute. The patients studied were those operated upon usually for focal epilepsy: there were 273 such operations on the dominant hemisphere and an equal number on the opposite side. The book opens with a brief discussion on the mind-brain relationship and a review of the cerebral basis of consciousness on lines which Penfield's work has already made familiar. There follows a historical review of aphasia, agnosia and apraxia, cerebral dominance and handedness. The reader is then given an account of the surgical procedure described as mapping the speech area and the results of electrical stimulations and localised cortical excision. Electrical stimulation may either cause vocalisation or interfere with speech. These interesting observations lead to the conclusion that "the left hemisphere is usually dominant for speech regardless of the handedness of the individual, with the exclusion of those who have cerebral injuries early in life." Cortical excisions often produce surprisingly little disturbance of speech when they might have been expected to do so. Nevertheless the authors believe that particular deficits in language may be shown to follow specific cortical removals, which they describe. Physiologically both receptive and expressive speech are held to depend upon interaction between the higher brain-stem, both cortical auditory areas and the left cerebral hemisphere. The final chapter on the learning of languages, in relation particularly to the age of the child, is an original and stimulating contribution to education.

It has clearly been impossible in a relatively short book, such as this, to do justice to the history of thought about aphasia and allied disturbances, or the complexities of psychophysiological theories about speech and its breakdown. What is valuable however, is the record of a unique series of original observations on the effects of cortical stimulation and cortical excision upon speech. There is nothing to suggest that the time has come when writers on aphasia will agree about its nature. Here, however, are new facts for their interpretation.

The book edited by Travis, whose personal contributions to the study of speech disturbances are well known, is a compendium of current knowledge about speech disorders at all functional levels. The scope of the book is so large that the treat-

XUM

ment of some topics is necessarily condensed. Part I, which includes articles on the development of speech, speech-sound formation and a long study of the acoustics of speech, will be particularly valuable to students of the subject who have not had time to keep up with the vast literature on these aspects of it. Part 2, dealing with speech and voice disorders associated with organic abnormalities, discusses amongst other things deafness and aphasia in both adults and children. Anatomical disorders, such as cleft palate and cleft lip, are also dealt with. Part 3 is mainly concerned with stuttering and Part 4 discusses psychotherapy and speech therapy, This encyclopædic volume will be useful to all who work in this field.

RUSSELL BRAIN.

The Development and Disorders of Speech in Childhood. By MURIEL E. MORLEY, B.Sc., F.C.S.T. Pp. 432. London: Livingstone. Price 45s.

As Professor Donald Court says in his foreword to this volume, "Speech is the most complicated, flexible and exciting instrument that man has created in his long social development." Consequently, it is not surprising that this faculty—one of the highest that has been attained in the animal kingdom—should suffer developmental abnormalities and that the anatomical structures and physiological mechanisms concerned with the understanding of language and the production of speech are sometimes faulty. Considering the importance of speech in all human affairs, the interest taken in speech disorders by the medical profession in general is not very considerable, while the subject finds little place in the medical student's curriculum. Miss Morley, however, has been fortunate in working with a pædiatrician—Professor Court—and a neurologist—Dr. Henry Miller—both of whom are interested in disturbances of speech, so that the Newcastle School is one of the best equipped in the country for dealing with such disorders. A work emanating from such a source should, therefore, be most instructive and Miss Morley's volume amply fufils this expectation.

Following a description of the normal development of speech in childhood, Miss Morley discusses the various disorders of the speech mechanism, her dissertation being based on a sample of children between the ages of 3 and 8 years; she also surveys in detail the incidence and types of speech disturbance in children of 5 to 15 years of age (school age) seen in the Newcastle upon Tyne Area. These observations lead to a relatively simple classification of speech disorders in children: (1) Disorders of language which include the aphasias, both receptive and executive or purely executive; alexia; agraphia; and also delayed development of speech associated with mental retardation or hearing deficiency. (2) Disorders of articulation, including anarthria, articulatory apraxia, dyslalia and various structural abnormalities such as cleft palate and dental irregularities. (3) Disorders of the utterance of speech, such as stammering and stuttering. (4) Disorders of voice (aphonia). Although comprehensive, this classification cannot yet be regarded as ideal. Among the disorders of language "congenital auditory imperception" might have been included as distinct from pure receptive aphasia, while it is doubtful if agraphia ever occurs as an isolated condition, being almost invariably associated with, and dependent upon, an alexia or dyslexia. "Dysarthria" is probably a better term than "anarthria," as the latter implies a complete absence of articulation; for the same reason one would prefer "dysphonia" to "aphonia." Also, among the developmental disorders of articulation one might now include "congenital suprabulbar paresis" and Mobiüs' and Evans' syndrome of cranial muscular (or nuclear) deficiencies.

Among the defects of articulation, the author distinguishes between "developmental dysarthria" and a condition termed "developmental articulatory apraxia"; it is admitted that the differential diagnosis is not always easy and that in some cases,

XUM

the response to treatment is the only means by which the diagnosis can be confirmed. As Miss Morley includes in the group of "developmental dysarthrias" those cases with signs of organic defects such as muscular spasticity and athetosis (conditions now usually classified under the heading of "cerebral palsy"), the differential diagnosis in most cases should not be difficult, for in articulatory apraxia there are no signs of organic disorder and no difficulty in spontaneous voluntary movement of the speech muscles; but they are not used correctly for articulation, either by imitation or spontaneously.

The clinical manifestations of the various forms of speech disorder are well described with numerous illustrative cases—if anything too many—and the various aspects of treatment are admirably presented.

Dyslalia is defined as a defect of articulation in which there is no abnormality of lips, tongue or palate, the defect being mainly one of consonant substitutions—and one might add syllabic omissions—speech being fluent even if unintelligible. Miss Morley states that the development of speech in such cases is not delayed. In many of the cases investigated, however, we have found that so-called dyslalia is frequently based on a delayed development of spoken language, that is a "developmental executive aphasia." The "dyslalias," however, are well worthy of further study.

Defects of speech due to various forms of partial deafness are reviewed and illustrative cases, together with audiograms, are described. Then follows a section on the defects of articulation due to structural abnormality such as cleft palate, short soft palate and palatal palsies. It is an academic point as to whether these disorders should be classified among the "dysphonias" rather than with articulatory defects. Other parts of the volume deal with stammering, speech disorder in twins, and lateral dominance in speech.

Miss Morley is to be congratulated on having produced a valuable contribution to the subject of speech disorders and one which provides a great deal of information to all interested in the subject, and which pædiatricians, neurologists, child psychologists, as well as speech therapists, might read with advantage.

C. WORSTER-DROUGHT.

TUMOURS OF THE NERVOUS SYSTEM

The Pathology of Tumours of the Nervous System. By DOROTHY S. RUSSELL, M.D., and L. J. RUBINSTEIN, M.D. Pp. 318. London: Edward Arnold. Price £3 10s.

By those who are acquainted with Professor Russell, the publication of this work has been awaited with pleasurable—even excited—anticipation. Her long and intense devotion to the subject, her wide experience based upon the work of a general hospital, and a maintained activity in general morbid anatomy, led one to expect an outstanding presentation of the subject. Her clarity of thought and of teaching and her early training in a department where her predecessor was noted for meticulously accurate observation seemed further guarantees of success. The book is all that one hoped for and more. It is written in beautiful English with a lucidity and succinctness which gives pleasure to the reader as well as information. Professor Russell has shared her task with Dr. Rubinstein and the uniform standard of style and of method of presentation clearly indicates that the authors worked together in great harmony. Though the task they shared was an exacting one, they can now look back on it with enjoyment and regard the volume with justifiable pride.

The preface states "We have sought to bring all aspects of our study fully up to date, to emphasize the more important biological aspects of the various abnormalities

XUM

discussed and to face existing difficulties of interpretation as frankly as possible." These three aims are exemplified throughout and are largely responsible for the great value of the book, particularly to neurosurgeons, and for making it so readable. The frequent brief references to individual case records, the intimate details about certain growths, the emphasis on the life history of the tumour, not only render descriptions vivid, but bring into the picture the patient who harboured the tumour. For the reviewer, the chapters on gliomas were of particular interest, and are perhaps the outstanding ones in the book. These tumours constitute a proverbially difficult subject viewed from the points of view of nomenclature, evolution and diagnostic presentation, but these difficulties are ironed out. One of these chapters is devoted to the important subject of growth and dissemination, an aspect which is so often ignored. It is, however, a disappointment to find that pituitary adenomas are virtually excluded, though tumours of the neurohypophysis are described. This is a deliberate decision by the authors and is explained in their introduction; it may be "logical" but most readers will doubtless consider it too purist an attitude, for these tumours inevitably and regularly come within the practice of neurologists and of neurosurgeons. A record of the authors' great experience would have been invaluable; perhaps they may be persuaded to remedy the deficiency in the next edition. In the last chapter Professor C. E. Lumsden gives an account of tissue culture, the aim being to describe the contribution that this technique provides to the biology of tumours of the nervous system. The choice of this subject with which to round off the work was most imaginative. Amongst other conclusions of general interest, Professor Lumsden considers that these special studies vindicate those who hold to the histogenetic system of classification, the arachnoidal origin of meningioma and the use of the term schwannoma.

However good the text may be, sufficient and clear illustrations are essential to a book of this nature. It is necessary therefore to record that the work is profusely illustrated, and the task of choosing the appropriate specimens must have been laborious, but the result for the reader is highly rewarding; each picture tells its tale. In this respect congratulations must be awarded to the technicians who have done their work so well. It is right also to accord praise to the work of the publishers and printers for the high standard which they have achieved. This is a volume which will become a classic in its subject, and will rapidly gain international fame.

Treatment of Cancer and Allied Diseases. Volume 2. *Tumours of Nervous System.* Ed. GEORGE T. PACK, M.D., and IRVING M. ARIEL, M.D. Pp. 316. London: Pitman Medical Publishing Co. Price £5 5s. 0d.

This volume suffers from the limitations imposed by its title. Treatment demands the exercise of judgment based upon accurate diagnosis and an assessment of what is possible in the particular patient, having regard to the nature of the tumour. Thus it is difficult to describe treatment alone except as an exercise in operative surgery and in radiotherapy. The contributors to this book have found this problem difficult to solve and this is manifest in overlapping and in uneven quality. The presentation in some chapters is that of diagnosis and treatment, with diagnosis being given either a prominent or a subservient role and in others the presentation is that of operative surgery; some are devoted to radiotherapy and these are mostly succinct accounts. The meningiomas (in 46 pages), the metastatic tumours (in 12 pages), and the spinal tumours (in 15 pages) are given excellent presentations of what are clearly the authors' wide experiences and well worth reading. Good accounts are also given of tumours of peripheral nerve and of the sympathetic ganglia and the paraganglionic cells. A first-rate description is given of pre- and post-operative care. In contrast, the section on congenital tumours covers 14 pages

XUM

of which only one and one half are concerned with treatment with little evidence of any personal experience. In another section, some curiously contradictory statements are found; thus quoting from successive paragraphs dealing with the radiotherapy of gliomas—"all forms of the gliomas show marked histologic evidence of regression after its use." "It is not certain that deep X-ray therapy increases the life-span of patients with glioblastoma, oligodendroglioma, astrocytoma or astroblastoma, because accurate control investigations cannot be established." Another cryptic remark from the same chapter "it is true that the gliomas are less likely to be completely removable than many other intracranial tumours, but it is gratifying nevertheless that many of them will be found to be satisfactorily removed, with long survival periods."

It is not often that a book can be criticized for having too many illustrations but in places in this volume the text is so divided by illustrations that they interfere seriously with reading and interest. The arrangement could have been improved, for example on one page there are only 4 lines above and 5 below an illustration. Some of the illustrations could have been omitted; for instance there seems little need to have 8 diagrams illustrating the seated position of the patient for a posterior fossa operation, or 9 photographs showing progress after facio-hypoglossal anastomosis. The editors could have given more precise instructions to their 30 authors and then used plenty of blue pencil to co-ordinate their contributions.

D. W. C. NORTHFIELD.

MONGOLISM

Der Mongolismus. By KARL KÖNIG. Pp. 278. Stuttgart: Hippokrates-Verlag.

Dr. König presents us with a modern version of the racial theory of mongolism. He regards the "mongol" as quite different from the ordinary forms of *homo sapiens* and as constituting a special type of man. In this connexion he uses the term "neoteny" indicating arrest at a larval stage of development. In his opinion the recently reported discovery of an additional chromosome in mongolism confirms his view. He goes on to say that neither an endocrine, nor any other biochemical defect is able to produce a new type of man but can only be the result of such a phenomenon. It is a little difficult to see how Dr. König's formulation helps the matter forward. It is now generally assumed that in phenylketonuria, tuberous sclerosis, gargoylism and Tay-Sachs' disease and in many other conditions producing mental defect there is a qualitative, if not quantitative alteration in the chromosomes whilst a change in chromosome number appears to be the cause of Turner's syndrome and other abnormalities of sex development. Are we to regard all these as new races of men? Likewise it is now considered that enzyme and metabolic changes derive directly from chromosome alterations and, in their turn, may lead to the anatomical and psychological peculiarities of the syndromes mentioned. It seems likely that this will prove to be the case in mongolism though the effect will be more diffuse inasmuch as an entire chromosome is involved, albeit a small one.

It is unlikely that Dr. König's view about the influence of the moon on the incidence of mongolism will receive general acceptance. The figures which he produces appear contradictory and, in any event, relate to date of birth of the children, whilst the abnormality will now in all probability be ascribed to a fault in maternal ovulation. Owing to the varying length of time between ovulation and conception and to the varying length of pregnancy any lunar influence on the birth date of mongols would surely be obscured.

Dr. König agrees that better diagnosis and less deaths in infancy have increased the number of "mongols" recognized. It is also only recently that reliable figures

XUM

on incidence at birth have become available so that there is little basis for comparison with earlier years or with other countries. In spite of this Dr. König feels that mongolism was in Seguin's time a rare disease which suddenly, in the middle of the last century, changed its nature, first of all in the British Isles whence it has spread in epidemic form over the entire earth.

The book is the result of intensive and careful study of the problem. It is well produced, with excellent photographs and many references. The unusual standpoint of the author is supported by numerous diagrams.

BRIAN HILLIARD.

NEUROSURGERY IN WAR

Surgery in World War II. Neurosurgery. Volume I. Prepared and published under the direction of Major-General S. B. Hays. Editors: Colonel John Boyd Coates, Jr., *M.C.*, R. Glen Spurling, M.D., Barnes Woodhall, M.D., Elizabeth M. McFetridge, M.A. Pp. 466. 133 Illustrations. Published by the Office of the Surgeon-General, Department of the Army, Washington, D.C., 1958. Price £1 18s. 6d.

This is the first of two volumes to be published which record the development of, and the part played by, the Neurosurgical Service of the American Army in the recent war, and is devoted to the organizational and administrative aspects of the service as well as with the practical treatment of injuries to the head, the second volume which is to appear later this year (1959) being left to deal with injuries to peripheral nerves and the spinal cord.

The book, which is the combined work of 14 neurosurgeons, was prepared and ready for printing in 1947—the same year that British Neurosurgical Experiences appeared in a War Supplement of the *British Journal of Surgery*—but its publication has been delayed until 1958, the original text, however, remaining unaltered.

In addition to a detailed and illustrated description of the surgical management of head wounds there are excellent chapters on blast-concussion, cranioplasty, post-traumatic epilepsy, disorders of speech, and a final pathological section dealing with the findings in 24 fatal cases of brain injury.

Appearing so long after the events with which it is concerned does not detract from its value, and it is salutary to note that the principles of surgical management of brain wounds evolved at that time remain unaltered and form the basis of present-day civilian practice. It is interesting at this stage to look back on and to compare the surgical methods adopted by the British and American neurosurgeons and to observe the remarkable uniformity of final opinion. It requires careful scrutiny to see any divergences, and those that do appear are merely nuances of inclination, the American preference perhaps being towards operating under local rather than general anæsthesia, to the repair and firm closure of the dura, and perhaps a more intensive search for, and removal of, the metallic foreign body.

Not the least interesting part of the book is that devoted to the organisation of the neurosurgical services, both in America and in the European theatres of war, which had to be done quickly and on a large scale. The method they adopted for producing the large number of neurosurgeons required was that of taking young general surgeons and giving them an intensive theoretical and practical course of neurosurgery, lasting four to six months, by which time they were capable of dealing with most types of head injuries under some degree of supervision, a method that seemed to work well and which the authors conclude could be applied to any specialty. The need for such a large number of neurosurgeons derived in part from the practice of posting a neurosurgeon to the fixed establishment of a large general hospital in the field which spent a lot of its time either closed or in transit, a practice that was very wasteful of

XUM

neurosurgical talent and which continued for a long time; rather than incorporating them, with an anæsthetist into small independent mobile groups.

This book provides an interesting historical record of American war neurosurgery and being an Army Medical Department publication its production is of course of a high quality with excellent illustrations and radiographic reproductions.

VALENTINE LOGUE.

PARKINSONISM

Pathogenesis and Treatment of Parkinsonism. Ed. W. S. FIELDS. Pp. 373. Oxford: Blackwell. Price 81s.

This symposium is compiled from papers and discussions at the 1958 annual scientific meeting of the Houston Neurological Society. The first part contains useful reviews of the experimental production of tremors and other forms of involuntary movement and their subsequent surgical relief. Kurland's paper dealing with the epidemiology and incidence of parkinsonism should be noted. He concludes that the incidence in the United States is about 1 : 4,000 of the total population, or 1 : 1,000 of those aged 50 or more, giving a total of some 266,000 living patients.

Alvord contributes a critical review of the pathology of parkinsonism which he has dedicated to the memory of the late Dr. Greenfield. While reaffirming that there are at least two types of the disease, the idiopathic and post-encephalitic forms, he makes clear that available pathological evidence is still very incomplete, notably in regard to adequate control material and the quantitative assessment of cellular degeneration in the basal ganglia and brain-stem. In essence, however, this review simply serves to underline Greenfield's conclusion that further anatomical and histological studies as such are unlikely to extend our knowledge of the pathogenesis of Parkinsonism.

Medical treatment receives scant attention in part II, though in the concluding section the role of surgery is discussed by a number of well-known neurosurgeons. There are fairly detailed reports of the contemporary onslaught on the globus pallidus and thalamus as well as useful reviews of some earlier surgical measures.

Though it contains little that is original, this book provides information upon a number of aspects of the disease, not least its surgical treatment. The results of making lesions of the globus pallidus or thalamus show that they may afford more profound and enduring relief from rigidity and tremor than that obtained by medical means alone, and that in selected patients the mortality and morbidity of the procedures used is low. Just what is actually done on these occasions as distinct from what the surgeon thinks he is doing is another matter and, as Bucy points out, adequate anatomical vertification of the site of these surgical lesions is rarely obtained. A plea for the collective pooling of such data was made at this conference, though it is gratifying to know that this step has already been taken in this country.

J. H. PATERSON.

AGEING

The Effect of Advancing Age upon the Human Spinal Cord. By L. RAYMOND MORRISON, M.D., with the collaboration of STANLEY COBB, M.D., and WALTER BAUER, M.D. 1959. Pp. 127. Oxford University Press. Price 48s.

No one can work for any time in the field of neuropathology without realizing how necessary it is to have an adequate knowledge of the normal appearance of the various components of the nervous system, and of the changes which result in the normal process of ageing. Only with a satisfactory basis for comparison can deduc-

XUM

tions be drawn about the possible pathological significance of minor deviations from the normal.

We must therefore appreciate the intention of Dr. Raymond Morrison in his efforts to provide us with information on the effects of ageing in the human spinal cord and acknowledge the work of Dr. Morrison's collaborators in completing and editing his manuscript after his death.

The book is divided into two parts. The first part is concerned with the histological appearance of the cord at representative cervical, thoracic and lumbar levels, in a series of patients of varying ages. The second part is in the form of an atlas showing the main features, as seen in transverse sections, of each segment of the cord in a 24-year-old woman.

The material which forms the basis for the study of the effect of ageing was derived from patients dying in a general hospital from such non-neurological diseases as malignant hypertension, rheumatic heart disease, cancer of the stomach, miliary tuberculosis, etc. The cases are considered in decades, from the second to the ninth. No specific mention is made of the diseases from which the patients in any one decade suffered, although casual mention of the "uremia" cases or the "lupus erythematous" case may be made. Changes are described in relation to the number of cases showing them and not in relation to the disease. For example, in the sixth decade there are 6 cases. It is stated in relation to the nerve cells of the anterior horn that "in one case they exhibit chronic shrinkage. . . . In 2 other cases the total volume of the cells is increased. . . . In 2 other cases there is early axonal reaction. . . ." In every group changes which are usually considered to be pathological are described.

In the discussion the points which appear to the authors to be characteristic of the ageing processes in the cord are discussed. Little attention is paid to the fact that the cords were derived from people who died from a disease process. The difficulty in obtaining *normal* tissue in man is great, but cords obtained from previous healthy individuals killed in road accidents and the like could have been interpreted much more confidently as showing the normal state of the C.N.S. uninfluenced by illness. A few years ago we were unaware of the neuropathological changes which might be found in patients with malignant disease of non-neurological organs. We still do not know what changes prolonged illness, cachexia or bed-sores may cause in the cord.

If more strictly normal material could not be obtained, the value of this book would have been greatly increased if the cause of death had been clearly stated in each case, and each cord had been described individually. The changes common to cords in any one decade might then have been distinguished from changes due to different diseases.

The second part of the book is based on the cord of a woman who died from subacute bacterial endocarditis. The cord was considered to be relatively normal, the only pathological feature being occasional foci of acute microglial infiltration. The characteristic outline of the grey matter in each segment is described, and the number of neurones in the larger groups of the anterior horn, of the lateral horn and of Clarke's column found in a ·25 mm. block is indicated. It is unfortunate that only the cell groups described by the earliest workers have been again considered, and that no attempt has been made to establish any figures for the number of neurones in the different parts of the posterior horn at different levels. In fact, this atlas adds little, if anything, to the classical atlas of Bruce, published in 1901.

As said at the beginning of this review, the endeavour to produce a control series of normal cords which would act as a basis for comparison with pathological cords of different ages is a commendable one, and it is only regrettable that this atlas does not achieve its aim.

MARION SMITH.

XUM

ALLERGIC ENCEPHALOMYELITIS

Allergic Encephalomyelitis. Ed. MARIAN W. KIES and ELLSWORTH C. ALVORD, Jr. 1959. Pp. 576. Charles C. Thomas, Springfield. Price £5 2s. 6d.

Like the shorter but otherwise similar volume devoted to Viral Encephalitis which was issued by the same publisher in 1958, the present book is based on the proceedings of a symposium, held in this instance at Bethesda in October 1957. It presents a comprehensive account of the encephalomyelitis which can be produced in experimental animals by the injection of brain emulsions, of the ways in which this disease can be employed as a laboratory tool, and of the possible implications of these studies in the field of human pathology.

The first chapter, by Roizin and Kolb, gives an excellent account of the histopathology of the experimental disease. Other aspects dealt with include rabies post-vaccinal encephalomyelitis in man (Shiraki), genetic factors and species differences (Schneider and Wolf), possible inter-relationships with spontaneously occurring human demyelinating diseases (Adams and Alvord), attempts at passive transfer and to identify the encephalitogenic substance or substances, and a survey of evidence for and against the allergic nature of the pathological processes involved.

The reader is taken to the fringe of advancing knowledge. Much of the experimental work described is unpublished elsewhere, much of the discussion is controversial and frankly speculative. The reviewer found it all immensely readable: the volume is beautifully produced and generously illustrated.

The observation that only a handful of the three-score contributors comes from Europe needs no emphasis. This book furnishes an eloquent expression of the dynamism which informs the best of American neurology, and shows how, in such hands, the subject is breaking through its traditional boundaries and exploiting the exciting discoveries presently being made in other fields of experimental medicine.

HENRY MILLER.

PSYCHIATRY

Traité de Psychiatrie. By HENRI BARUK. 2 vols. 1958. Pp. 1570. Paris: Masson & Cie. Fr. 13,400.

Professor Baruk, as this monumental work attests, belongs to the heroic age. His treatise, embracing almost the whole of psychiatry, bespeaks the personal labours and the individual outlook of a man who has ploughed his own furrow for more than thirty years. Not that Professor Baruk is indifferent to the strong currents of French psychiatry from the time of Pinel: indeed to an English psychiatrist he seems penetrated through and through with the French tradition. His own investigations and experience, however, have coloured his outlook deeply. His study of the mental accompaniments of cerebral tumour in 1924 and 1925 at the Salpêtrière and in Clovis-Vincent's wards led to a detailed study of the differences between the psychological effects of prefrontal and temporal lesions and the symptoms of the major psychoses. His inquiries into experimental catatonia kindled his interest in the way diffuse extracerebral disturbances could bring about severe neurological and psychological disorder. From this grew his pharmacological experiments, pursued with renewed energy during the last few years. He has become convinced that along with physiological advances must come progress in clinical differentiation, and a new nosography and pathology. Parallel with all this he has, for twenty years, insisted that the moral aspects of human behaviour fall within the psychiatrist's scope. Honesty, hate, justice and culpability are concepts he has endeavoured to elucidate, believing them essential to any unitary view of man living through time. How far Professor Baruk has succeeded in his gallant undertaking can be judged only in relation to his difficulties: his originality, however, is hardly to be disputed.

XUM

These two massive volumes, containing 1,570 pages, cannot be briefly reviesed nor their contents fully listed. The first volume describes the major syndromes, after an introductory section on personality and on methods of examination in which Dr. Baruk includes his Tsedek test of moral and other value judgments. The second volume is devoted to treatment and the organic syndromes. Its penultimate chapter deals with the problem of consciousness; the last chapter is called "Psychiatric Humanism" and concludes with an eloquent and detailed exposition of the method of treatment which Dr. Baruk calls *chitamnie* or trust-therapy.

Though idiosyncratic and remote in many respects from prevailing Anglo-American psychiatric thought, this treatise has a unitary sweep and courage which makes it well worth the attention of English-speaking psychiatrists.

AUBREY LEWIS.

Mental Illness in London. By VERA NORIS. 1959. Pp. 317. London: Chapman and Hall. Price 35s.

This is the sixth of the Maudsley Monographs, and more than maintains the standard of the series. The late Dr. Vera Norris, who died in September 1957, was a gifted worker who approached the collection and the interpretation of statistical data with both common sense and imagination. This volume gives an account of the way in which case data, relating to approximately 10,000 patients admitted to psychiatric hospitals of the London area between 1947 and 1949, could be explored for findings of epidemiological and sociological interest. Even basic questions of diagnostic validity could be investigated, as is shown for instance by a study of the extent to which different diagnoses were retained on passing from one hospital to another.

The work is not only an account of results obtained, but is also of great methodological interest. Later workers who have to busy themselves with the same problems will find a critical account of the methods available, with pointers to sources of error.

ELIOT SLATER.

HISTORY OF NEUROLOGY

The History and Philosophy of Knowledge of the Brain and its Functions. Ed. F. N. L. POYNTER, Ph.D., F.L.A. 1958. Pp. 272. Oxford: Blackwell. Price 22s. 6d.

This symposium was planned as an historical introduction to the First International Congress of Neurological Sciences. It was sponsored by the Wellcome Foundation. The book begins with a Foreword by the Chairman of the Wellcome Foundation and ends with an address by Sir Henry Dale. The book is difficult to review, for the essays reflect the personal neurological interest of authorities in very diverse fields,—so diverse in content are the papers that the title of each and its author is given:

First Session.—Hippocratic preamble: The brain and intelligence: Wilder Penfield. Concepts of the brain and its functions in classical antiquity: D. H. M. Woollam. Body and soul in Aristotelian tradition: J. S. Wilkie. Non-Western concepts of psychic function: Ilaz Veith.

Second Session.—The origins of language: Macdonald Critchley. Old and new concepts of the basis of consciousness: Denis Williams. Hughlings Jackson's ideas of consciousness in the light of today: Sir Russell Brain.

Third Session.—Medieval and renaissance contributions to knowledge of the brain and its functions: Walter Pagel. Descartes's ideas of brain function: Walther

Riese. Wars of ideas in neurological science—from Willis to Bichat and from Locke to Condillac: W. P. D. Wightman.

Fourth Session.—Contributions of Gall and the prenologists to knowledge of brain function: Erwin H. Ackerknecht. J. C. Reil's concepts of brain function: Sir Aubrey Lewis. Chemical contributions, especially from the nineteenth century, to knowledge of the brain and its functioning: Henry McIlwain.

Fifth Session.—The evolution of concepts relating to the electrical activity of the nervous system: M. A. B. Brazier. Some reflections upon the opening phase of the physiology of the cerebral cortex: Sir Francis Walshe. Current developments in thought and the past evolution of ideas concerning integrative function: Chandler McC. Brooks.

Those contributors whose breadth of interest in neurological history and philosophy is most sincere and extensive have produced the most effective and satisfying creations. Several essays show a very personal style of thoughtfulness, scholarship and polish. In another, a negligible philosophy combines with an insensibility of the high standard required for the occasion.

This book stimulates that historical sense which, even more in neurophysiology than in neurology, is required as a corrective of the inco-ordinations and imbalance induced by ephemeral fashions. We forget (or were never obliged to realize) how many times new forms of experiment and explanation seemed to have settled certain fundamental problems, only later to suffer in turn their decline and fall.

Perhaps the main interest and importance of this collection of essays will be its value for historians and philosophers of the future. Even though time, as Dr. Penfield suggests, may "wash away the patterns of our present thinking" in so far as they guide professional behaviour and clinical research, these essays will remain as an important statement of mid-twentieth century neurological trends, beliefs, and hopes.

The moral of the book may be expressed in a quotation from it: "There is one modest lesson we might learn from history, and that is the vital necessity of the fullest possible exchange of knowledge and opinion between clinical and experimental observers."

WILLIAM GOODDY.

William Harvey de Motu Locali Animalium 1627. Edited, translated and introduced by GWENETH WHITTERIDGE, M.A., D.Phil., F.S.A. Archivist of St. Bartholomew's Hospital, London. 1959. Pp. 163. Cambridge University Press. Price 60s.

This is a hitherto unpublished book by William Harvey consisting of the manuscript notes for a treatise he intended to write on muscular action and the movement of animals. Dr. Whitteridge has performed with great skill the triple task of deciphering and transcribing Harvey's obscure handwriting, translating his Latin, and tracing the sources of his ideas. Much of the work is a restatement, with Harvey's comments, of the traditional concepts derived from Aristotle, Galen and Harvey's more immediate predecessors. It gains freshness from illustrations chosen from the behaviour of birds, fish and insects. Harvey's attempts to apply his neurophysiology to clinical problems of disorder of movement in man are tantalizingly brief, but sufficient to show that he was keenly alive to both physiological and clinical neurology. This book illuminates Harvey and throws a sidelight on the history of neurology in the seventeenth century.

XUM

SHORTER NOTICES

Molecules and Mental Health. Ed. FREDERICK A. GIBBS, M.D., Professor of Neurology, University of Illinois. Pp. 189. Lippincott: Philadelphia. (No price given.)

The Brain Research Foundation was founded recently by Dr. Gibbs, and two colloquia have been held, the first on amides in relation to brain function and behaviour and the second on the effect of corticosteroids on the disorder with retardation, myoclonus and massive spasms seen in infants and called hypsarhythmia by Dr. Gibbs. The papers presented are of a high order, of particular value to those who study the physical basis of the psychoses including schizophrenia.

The History and Origin of Language. By A. S. DIAMOND, LL.D. London: Methuen. Pp. 280. Price 30s.

Dr. Diamond considers the history of the sounds of language and their meanings against their syntactical background. The structure of words and sentences in living and dead languages are used by him to trace their evolution in man, and that evolution is only secondarily related by him to its neural basis. Meaningful sound and gesture in animals is related to the theories surrounding the beginnings of speech in man. In short, the student of the functions of the nervous system will enjoy the book as "an intelligent layman," for whom it is written. He will find the grammatical analysis heavy going, and the neurology simple, but the historical fact and theory quite enthralling.

THE COMMISSION OF NEUROCHEMISTRY OF THE WORLD FEDERATION OF NEUROLOGY

THE Commission of Neurochemistry of the World Federation of Neurology met for the first time at the Institut Bunge in Antwerp, Belgium, on September 29 and 30, 1959. Dr. Ludo van Bogaert, President of the Federation and Dr. Charles Poser, Medical Executive Officer, assisted at the meeting.

The following neurochemists had been invited and constituted the original Commission:

DR. BAUER, *Hamburg, Germany;* DR. BRANTE, *Eskilstuna, Sweden;* DR. CUMINGS, *London, England;* DR. EDGAR, *Amsterdam, Netherlands;* DR. FOLCH-PI, *Waverley, Mass., U.S.A.;* DR. KOREY, *New York, U.S.A.;* DR. LOWENTHAL, *Antwerp, Belgium;* DR. PEARSE, *London, England;* DR. QUASTEL, *Montreal, Canada;* DR. RICHTER, *Cardiff, England;* DR. SVENNERHOLM, *Göteborg, Sweden;* DR. TOURTELOTTE, *Ann Arbor, Mich., U.S.A.*

The Commission discussed the participation of neurochemists in the different international congresses. A permanent secretariat is to be established at the Institut Bunge, in Antwerp. Dr. A. Lowenthal was named Secretary of the Commission.

Plans were laid for holding a Symposium on Neurochemistry in Rome during the Congress of Neurology of 1961. The two major topics to be covered are: (1) Lipids, lipoproteins and their metabolism; (2) Disorders of myelin (not including disseminated sclerosis).

The Commission plans to establish a Registry of neurological material available for neurochemical investigation. In the near future, it is hoped that neurological associations and neuropathological centres will be informed of the type of material wanted by the neurochemists and under what conditions this material is to be obtained and shipped. All requests and inquiries are to be addressed to the Secretary of the Commission who will see to it that the necessary contacts are made between physicians offering material and those requesting it for chemical study. It should be understood that although collaborative efforts are encouraged, each investigator retains full publication rights concerning the material he furnishes.

The Secretary of the Commission will endeavour to keep the various medical and scientific journals informed about the activities of the Commission and welcomes any suggestions from interested physicians.

THE CENTENARY OF THE NATIONAL HOSPITAL, QUEEN SQUARE

THE National Hospital, Queen Square, will be celebrating its centenary in 1960 from June 20–25. The occasion will be marked by neuro-historical presentations, as well as by a wide range of social functions. Personal invitations are in the course of being sent to every former student and house officer at the hospital. In addition, the hospital will be extending a most cordial welcome to neurologists, neurosurgeons and others, to participate in these activities. An *ad hoc* notice will be forwarded not only to individuals who have worked at Queen Square, but to all official neurological and neurosurgical Societies. For details, apply to Dr. Macdonald Critchley, National Hospital, Queen Square, London, W.C.1.

XUM

INDEX

TO

BRAIN:

A JOURNAL OF NEUROLOGY,

FOR

VOL. LXXXII, 1959

AUTHORS

PAGE

Allison, R. S., Millar, J. H. D., Cheeseman, E. A., and Merrett, J. D.
Pregnancy as a Factor Influencing Relapse in Disseminated Sclerosis .. 417

Barton, A. A., and Causey, G.
The Cellular Content of the Endoneurium of Peripheral Nerve 594

Bender, M. B., and Shanzer, S.
Oculomotor Responses on Vestibular Stimulation of Monkeys with Lesions of the Brain-stem 669

Bligh, A. S., Wells, C. E. C., and Spillane, J. D.
The Cervical Spinal Canal in Syringomyelia 23

Bogaert, L. van, and Poser, C. M.
Neuropathologic Observations in Phenylketonuria 1

Botez, M. I., and Wertheim, N.
Expressive Aphasia and Amusia Following Right Frontal Lesion in a Right-handed Man.. 186

Brain, R., and Wilkinson, M.
Observations on the Extensor Plantar Reflex and Its Relationship to the Functions of the Pyramidal Tract, with Special Reference to (1) the Plantar Reflex in Infancy, (2) the Crossed Extensor Plantar Reflex and (3) Extension of the Great Toe as an Associated Movement .. 297

Bull, J. W. D., Nixon, W. L. B., Pratt, R. T. C., and Robinson, P. K.
Paget's Disease of the Skull and Secondary Basilar Impression 10

Causey, G., and Barton, A. A.
The Cellular Content of the Endoneurium of Peripheral Nerve 594

Cavanagh, J. B., and Falconer, M. A.
Clinico-pathological Considerations of Temporal Lobe Epilepsy Due to Small Focal Lesions. A Study of Cases Submitted to Operation .. 483

XUM

PAGE

Cheeseman, E. A., Millar, J. H. D., Allison, R. S., and Merrett, J. D.
Pregnancy as a Factor Influencing Relapse in Disseminated Sclerosis .. 417

Clare, M. H., and Landau, W. M.
The Plantar Reflex in Man with Special Reference to Some Conditions where the Extensor Response is Unexpectedly Absent 321

Crompton, M. R.
The Visual Changes in Temporal (Giant-cell) Arteritis. Report of a Case with Autopsy Findings 377

Day, W. R.
Casts of Fœtal Lateral Ventricles 109

Douglass, E., and Richardson, J. C.
Aphasia in a Congenital Deaf-mute 68

Downer, J. L. de C.
Changes in Visually Guided Behaviour Following Midsagittal Division of Optic Chiasm and Corpus Callosum in Monkey (*Macaca Mulatta*) .. 251

Engel, W. K., Kurland, L. T., and Klatzo, I.
An Inherited Disease Similar to Amyotrophic Lateral Sclerosis with a Pattern of Posterior Column Involvement. An Intermediate Form? 203

Ettlinger, G.
Visual Discrimination Following Successive Temporal Ablations in Monkeys 232

Falconer, M. A., and Cavanagh, J. B.
Clinico-pathological Considerations of Temporal Lobe Epilepsy Due to Small Focal Lesions. A Study of Cases Submitted to Operation .. 483

Goldie, L., and Green, J. M.
A Study of the Psychological Factors in a Case of Sensory Reflex Epilepsy 505

Goldstein, N. P., Hill, N. C., McKenzie, B. F., McGuckin, W. F., and Svien, H. J.
Cerebrospinal-fluid Proteins, Glycoproteins, and Lipoproteins in Obstructive Lesions of the Central Nervous System 581

Gordon, N., and Hudson, R. E. B.
Refsum's Syndrome—Heredopathia Atactica Polyneuritiformis. A Report of Three Cases, Including a Study of the Cardiac Pathology.. .. 41

Green, J. M., and Goldie, L.
A Study of the Psychological Factors in a Case of Sensory Reflex Epilepsy 505

Hebb, D. O.
Intelligence, Brain Function and the Theory of Mind 260

Hierons, R., and Lyle, T. K.
Bilateral Retrobulbar Optic Neuritis 56

Hill, N. C., Goldstein, N. P., McKenzie, B. F., McGuckin, W. F., and Svien, H. J.
Cerebrospinal-fluid Proteins, Glycoproteins, and Lipoproteins in Obstructive Lesions of the Central Nervous System 581

Howell, D. A.
Upper Brain-stem Compression and Foraminal Impaction with Intracranial Space-occupying Lesions and Brain Swelling 525

XUM

PAGE

Hudson, R. E. B., and Gordon, N.
Refsum's Syndrome—Heredopathia Atactica Polyneuritiformis. A Report of Three Cases, Including a Study of the Cardiac Pathology 41

Huszák, I., and Széchenyi
The Disturbance of the Metabolism of Keto-bodies in Multiple Sclerosis 427

Ingram, T. T. S.
Specific Developmental Disorders of Speech in Childhood.. 450

Kennedy, W. A.
Clinical and Electroencephalographic Aspects of Epileptogenic Lesions of the Medial Surface and Superior Border of the Cerebral Hemisphere 147

Klatzo, I., Engel, W. K., and Kurland, L. T.
An Inherited Disease Similar to Amyotrophic Lateral Sclerosis with a Pattern of Posterior Column Involvement. An Intermediate Form? 203

Kurland, L. T., Engel, W. K., and Klatzo, I.
An Inherited Disease Similar to Amyotrophic Lateral Sclerosis with a Pattern of Posterior Column Involvement. An Intermediate Form? 203

Landau, W. M., and Clare, M. H.
The Plantar Reflex in Man with Special Reference to Some Conditions where the Extensor Response is Unexpectedly Absent 321

Laurence, K. M.
Some Applications of the Urinary Phenolsulphonphthalein Excretion Test in Hydrocephalus and Related Conditions 551

Leyburn, P., and Walton, J. N.
The Treatment of Myotonia: A Controlled Clinical Trial 81

Luria, A. R.
Disorders of "Simultaneous Perception" in a Case of Bilateral Occipito-parietal Brain Injury 437

Lyle, T. K., and Hierons, R.
Bilateral Retrobulbar Optic Neuritis 56

McCaul, I. R., and Martin, J. P.
Acute Hemiballismus Treated by Ventrolateral Thalamolysis 104

McGuckin, W. F., Hill, N. C., Goldstein, N. P., McKenzie, B. F., and Svien, H. J.
Cerebrospinal-fluid Proteins, Glycoproteins, and Lipoproteins in Obstructive Lesions of the Central Nervous System 581

McIntyre, A. K., and Robinson, R. G.
Pathway for the Jaw-jerk in Man 468

McKenzie, B. F., Hill, N. C., Goldstein, N. P., McGuckin, W. F., and Svien, H. J.
Cerebrospinal-fluid Proteins, Glycoproteins, and Lipoproteins in Obstructive Lesions of the Central Nervous System 581

McKissock, W., and Paine, K. W. E.
Subarachnoid Hæmorrhage 366

Marshall, J.
Observations on Endocrine Function in Dystrophia Myotonica 221

Marshall, R. D., Sunderland, S., and Swaney, W. E.
The Intraneural Topography of the Circumflex, Musculocutaneous and Obturator Nerves 116

XUM

PAGE

Martin, J. P., and McCaul, I. R.
Acute Hemiballismus Treated by Ventrolateral Thalamolysis 104

Merrett, J. D., Millar, J. H. D., Allison, R. S., and Cheeseman, E. A.
Pregnancy as a Factor Influencing Relapse in Disseminated Sclerosis .. 417

Meyer, J. S., and Portnoy, H. D.
Post-epileptic Paralysis. A Clinical and Experimental Study 162

Millar, J. H. D., Allison, R. S., Cheeseman, E. A., and Merrett, J. D.
Pregnancy as a Factor Influencing Relapse in Disseminated Sclerosis .. 417

Nathan, P. W., and Smith, M. C.
Fasciculi Proprii of the Spinal Cord in Man. Review of Present Knowledge 610

Nixon, W. L. B., Bull, J. W. D., Pratt, R. T. C., and Robinson, P. K.
Paget's Disease of the Skull and Secondary Basilar Impression 10

Oswald, I.
Sudden Bodily Jerks on Falling Asleep 92

Paine, K. W. E., and McKissock, W.
Subarachnoid Hæmorrhage 356

Pedersen, E.
Epidemic Vertigo: Clinical Picture, Epidemiology and Relation to Encephalitis.. 566

Portnoy, H. D., and Meyer, J. S.
Post-epileptic Paralysis. A Clinical and Experimental Study 162

Poser, C. M., and Bogaert, L. van
Neuropathologic Observations in Phenylketonuria 1

Potter, J. M.
Redistribution of Blood to the Brain Due to Localized Cerebral Arterial Spasm: the Possible Importance of Small Peripheral Anastomotic Cerebral Arteries 367

Pratt, R. T. C., Bull, J. W. D., Nixon, W. L. B., and Robinson, P. K.
Paget's Disease of the Skull and Secondary Basilar Impression 10

Richardson, J. C., and Douglass, E.
Aphasia in a Congenital Deaf-mute 68

Roberts, P. D.
Familial Calcification of the Cerebral Basal Ganglia and Its Relation to Hypoparathyroidism 599

Robinson, P. K., Bull, J. W. D., Nixon, W. L. B., and Pratt, R. T. C.
Paget's Disease of the Skull and Secondary Basilar Impression 10

Robinson, R. G., and McIntyre, A. K.
Pathway for the Jaw-jerk in Man 468

Shanzer, S., and Bender, M. B.
Oculomotor Responses on Vestibular Stimulation of Monkeys with Lesions of the Brain-stem 669

Smith, M. C., and Nathan, P. W.
Fasciculi Proprii of the Spinal Cord in Man. Review of Present Knowledge 610

Spillane, J. D., and Wells, C. E. C.
Isolated Trigeminal Neuropathy. A Report of 16 Cases 391

PAGE

Spillane, J. D., Wells, C. E. C., and Bligh, A. S.
The Cervical Spinal Canal in Syringomyelia 23

Sunderland, S., Marshall, R. D., and Swaney, W. E.
The Intraneural Topography of the Circumflex, Musculocutaneous and Obturator Nerves 116

Svien, H. J., Hill, N. C., Goldstein, N. P., McKenzie, B. F., and McGuckin, W. F.
Cerebrospinal-fluid Proteins, Glycoproteins, and Lipoproteins in Obstructive Lesions of the Central Nervous System 581

Swaney, W. E., Sunderland, S., and Marshall, R. D.
The Intraneural Topography of the Circumflex, Musculocutaneous and Obturator Nerves 116

Symonds, C.
Excitation and Inhibition in Epilepsy 133

Széchenyi, and Huszák, I.
The Disturbance of the Metabolism of Keto-bodies in Multiple Sclerosis 427

Walton, J. N., and Leyburn, P.
The Treatment of Myotonia: A Controlled Clinical Trial 81

Wells, C. E. C., and Spillane, J. D.
Isolated Trigeminal Neuropathy. A Report of 16 Cases 391

Wells, C. E. C., Spillane, J. D., and Bligh, A. S.
The Cervical Spinal Canal in Syringomyelia 23

Wertheim, N., and Botez, M. I.
Expressive Aphasia and Amusia Following Right Frontal Lesion in a Right-handed Man 186

Wilkinson, M., and Brain, R.
Observations on the Extensor Plantar Reflex and Its Relationship to the Functions of the Pyramidal Tract, with Special Reference to (1) the Plantar Reflex in Infancy, (2) the Crossed Extensor Plantar Reflex and (3) Extension of the Great Toe as an Associated Movement .. 297

Wolman, L.
Cerebral Dissecting Aneurysms 276

XUM

SUBJECTS

PAGE

Amyotrophic Lateral Sclerosis, An Inherited Disease Similar to, with a Pattern of Posterior Column Involvement. An Intermediate Form? W. K. Engel, L. T. Kurland and I. Klatzo 203

Aneurysms, Cerebral Dissecting. L. Wolman 276

Aphasia, Expressive, and Amusia, Following Right Frontal Lesion in a Right-handed Man. M. I. Botez and N. Wertheim 186

Aphasia in a Congenital Deaf-mute. E. Douglass and J. C. Richardson .. 68

Behaviour, Visually Guided, Changes in, Following Midsagittal Division of Optic Chiasm and Corpus Callosum in Monkey (*Macaca Mulatta*). J. L. de C. Downer 251

Brain-stem, Upper, Compression, and Foraminal Impaction with Intracranial Space-occupying Lesions and Brain Swelling. D. A. Howell 525

Cerebral Arterial Spasm, Localized, Redistribution of Blood to the Brain Due to. The Possible Importance of the Small Peripheral Anastomotic Cerebral Arteries. J. M. Potter 367

Cerebral Basal Ganglia, Familial Calcification of the, and Its Relation to Hypoparathyroidism. P. D. Roberts 599

Cerebrospinal-fluid Proteins, Glycoproteins, and Lipoproteins in Obstructive Lesions of the Central Nervous System. N. C. Hill, N. P. Goldstein, B. F. McKenzie, W. F. McGuckin and H. J. Svien 581

Disseminated Sclerosis, Pregnancy as a Factor Influencing Relapse in. J. H. D. Millar, R. S. Allison, E. A. Cheeseman and J. D. Merrett 417

Dystrophia Myotonica, Observations on Endocrine Function in. J. Marshall .. 221

Endoneurium of Peripheral Nerve, The Cellular Content of the. G. Causey and A. A. Barton 594

Epilepsy, Excitation and Inhibition in. C. Symonds 133

Epilepsy, Sensory Reflex, A Study of the Psychological Factors in a Case of. L. Goldie and J. M. Green 505

Epileptogenic Lesions of the Medial Surface and Superior Border of the Cerebral Hemisphere, Clinical and Encephalographic Aspects of. W. A. Kennedy 147

Fasciculi Proprii of the Spinal Cord in Man. Review of Present Knowledge. P. W. Nathan and M. C. Smith 610

Hemiballismus, Acute, Treated by Ventrolateral Thalamolysis. J. P. Martin and I. R. McCaul 104

Hydrocephalus and Related Conditions, Some Applications of the Urinary Phenolsulphonphthalein Excretion Test in. K. M. Laurence 551

Intelligence, Brain Function and the Theory of Mind. D. O. Hebb 260

Jaw-jerk in Man, Pathway for the. A. K. McIntyre and R. G. Robinson .. 468

Jerks, Sudden Bodily, on Falling Asleep. I. Oswald 92

Lateral Ventricles, Fœtal Casts of. W. R. Day 109

Multiple Sclerosis, The Disturbance of the Metabolism of Keto-bodies in. I. Huszák and Széchenyi 427

Myotonia, The Treatment of: A Controlled Clinical Trial. P. Leyburn and J. N. Walton 81

XUM

PAGE

Nerves, Circumflex, Musculocutaneous and Obturator, The Intraneural Topography of the. S. Sunderland, R. D. Marshall and W. E. Swaney .. 116

Paget's Disease of the Skull and Secondary Basilar Impression. J. W. D. Bull, W. L. B. Nixon, R. T. C. Pratt and P. K. Robinson 10

Phenylketonuria, Neuropathologic Observations in. C. M. Poser and L. van Bogaert 1

Plantar Reflex, the Extensor, Observations on, and Its Relationship to the Functions of the Pyramidal Tract, with Special Reference to (1) the Plantar Reflex in Infancy, (2) the Crossed Extensor Plantar Reflex and (3) Extension of the Great Toe as an Associated Movement. R. Brain and M. Wilkinson 297

Plantar Reflex, The, in Man. With Special Reference to Some Conditions where the Extensor Response is Unexpectedly Absent. W. M. Landau and M. H. Clare 321

Post-epileptic Paralysis. A Clinical and Experimental Study. J. S. Meyer and H. D. Portnoy 162

Refsum's Syndrome—Heredopathia Atactica Polyneuritiformis. A Report of Three Cases, Including a Study of the Cardiac Pathology. N. Gordon and R. E. B. Hudson.. 41

Retrobulbar Optic Neuritis, Bilateral. R. Hierons and T. K. Lyle 56

"Simultaneous Perception," Disorders of, in a Case of Bilateral Occipito-parietal Brain Injury. A. R. Luria 437

Speech, Specific Developmental Disorders of, in Childhood. T. T. S. Ingram 450

Subarachnoid Hæmorrhage. W. McKissock and K. W. E. Paine 356

Syringomyelia, The Cervical Spinal Canal in. C. E. C. Wells, J. D. Spillane and A. S. Bligh 23

Temporal (Giant-cell) Arteritis, The Visual Changes in. Report of a Case with Autopsy Findings. M. R. Crompton 377

Temporal Lobe Epilepsy Due to Small Focal Lesions, Clinico-pathological Considerations of. A Study of Cases Submitted to Operation. M. A. Falconer and J. B. Cavanagh 483

Trigeminal Neuropathy, Isolated. A Report of 16 Cases. J. D. Spillane and C. E. C. Wells 391

Vertigo, Epidemic: Clinical Picture, Epidemiology and Relation to Encephalitis. E. Pedersen 566

Vestibular Stimulation of Monkeys with Lesions of the Brain-stem, Oculomotor Responses on. S. Shanzar and M. B. Bender 669

Visual Discrimination Following Successive Temporal Ablations in Monkeys. G. Ettlinger 232

XUM

NOTICES OF RECENT PUBLICATIONS

	PAGE
The Epileptic Seizure. Its Functional Morphology and Diagnostic Significance. C. Ajmone-Marsan and B. L. Ralston. 1957	477
Temporal Lobe Epilepsy. Edited by M. Baldwin and P. Bailey. 1958	477
Traité de Psychiatrie. 2 vols. H. Baruk. 1958	691
L'Angiographie Cérébrale. J. Bonnal and J. Legré	132
The Nature of Experience. Riddell Memorial Lectures. Thirtieth Series. Sir Russell Brain. 1959	292
Liver-Brain Relationships. I. A. Brown. 1957	295
Surgery in World War II. Neurosurgery. Vol. I. Edited by J. B. Coates, Jr., R. G. Spurling, B. Woodhall and E. M. McFetridge. 1958	688
Amphetamine Psychosis. P. H. Connell. 1958	130
Introduzione alla Elettroencefalografia Clinica. G. M. Corsino. 1957	482
Thérapeutique Neurologique et Psychiatrique. P. Cossa. 1958	132
The Mentally Retarded in Society. S. P. Davies. 1959	476
Cranio-cerebral Topometry in Man. A. Delmas and B. Pertuiset. 1959	131
The History and Origin of Language. A. S. Diamond	694
Electronic Apparatus for Biological Research. P. E. K. Donaldson. 1958	478
Thudichum, Chemist of the Brain. D. L. Drabkin. 1958	480
Perceptual Processes and Mental Illness. H. J. Eysenck, G. W. Ganger and J. C. Brengelmann. 1957	293
Pathogenesis and Treatment of Parkinsonism. Edited by W. S. Fields. 1958	689
Molecules and Mental Health. Edited by F. A. Gibbs	694
Epilepsy Handbook. F. A. Gibbs and F. W. Stamps. 1958	296
Henry Ford Hospital International Symposium. Reticular Formation of the Brain. Edited by H. H. Jasper, L. D. Proctor, R. S. Knighton, W. C. Noshay and R. T. Costello. 1958	475
Allergic Encephalomyelitis. Edited by M. W. Kies and E. C. Alvord, Jr. 1959	691
Der Mongolismus. K. Knöig	687
Grosse Nervenarzte. Bd. 2. Edited by K. Kolle. 1959	296
Die Neuroallergischen Beziehungen in der Histopathologie der Multiplen Sklerose. T. Lehoczky. 1957	476
Therapeutic Exercise. Edited by S. Licht. 1958	295
Manuel Pratique du Test de Rorschach. M. Loosli-Usteri	293
The Waking Brain. H. W. Magoun. 1958	475
The Sella in Health and Disease. *British Journal of Radiology*, Supp. 8. M. El Sayed Mahmoud. 1958.	132
A Textbook of Neurology. 2nd edition. H. H. Merritt. 1959	482
The Development and Disorders of Speech in Childhood. M. E. Morley. 1957	683
The Effect of Advancing Age upon the Human Spinal Cord. L. R. Morrison, with the collaboration of S. Cobb and W. Bauer. 1959	689
Psychiatry in Medical Practice. Edited by W. L. Neustatter. 1958	481

XUM

PAGE

Mental Illness in London. V. Noris. 1959 692

Treatment of Cancer and Allied Diseases. Vol. 2. Tumors of the Nervous System. Edited by G. T. Pack and I. M. Ariel. 1958 686

The Excitable Cortex in Conscious Man. The Fifth Sherrington Lecture. W. Penfield. 1958 132

Speech and Brain-Mechanisms. W. Penfield and L. Roberts. 1959 683

The History and Philosophy of Knowledge of the Brain and its Functions. Edited by F. N. L. Poynter. 1958 692

A History of Neurology. W. Riese. 1959 296

The Pathology of Tumours of the Nervous System. D. S. Russell and L. J. Rubinstein. 1959 685

Brain. Memory and Learning. A Neurologist's View. R. Russell 479

Epilepsy. M. Sakel. 1959 130

Schizophrenia. M. Sakel. 1958 481

Psychopathic Personalities. K. Schneider. 1958 482

Diagnostic Performance Tests. B. Semeonoff and E. Trist 293

External Collimation Detection of Intracranial Neoplasia with Unstable Nuclides. G. M. Shy, R. B. Bradley and W. B. Matthews. 1958 294

L'Exploration Chirurgicale Stéréotaxique du Lobe Temporal dans l'Epilepsie Temporale. Repérage Anatomique Stéréotaxique et Technique Chirurgicale. J. Talairach, P. Tournoux and M. David 131

Handbook of Speech Pathology. Edited by L. E. Travis. 1959 683

Les Maladies Nerveuses. 7th edition. A. van Gehuchten 132

Diseases of the Nervous System. 9th edition. Sir Francis Walshe. 1958 .. 132

Polymyositis. J. N. Walton and R. D. Adams. 1958 480

Psychiatry in General Practice. J. A. Weijel. 1958 481

William Harvey de Motu Locali Animalium 1627. Edited by G. Whitteridge. 1959 693

Neurological and Psychological Deficits of Asphyxia Neonatorum, with consideration of use of primates for experimental investigations. Edited by W. F. Windle. 1958 481

XUM